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VOLUME 99(8) — AUGUST 1990

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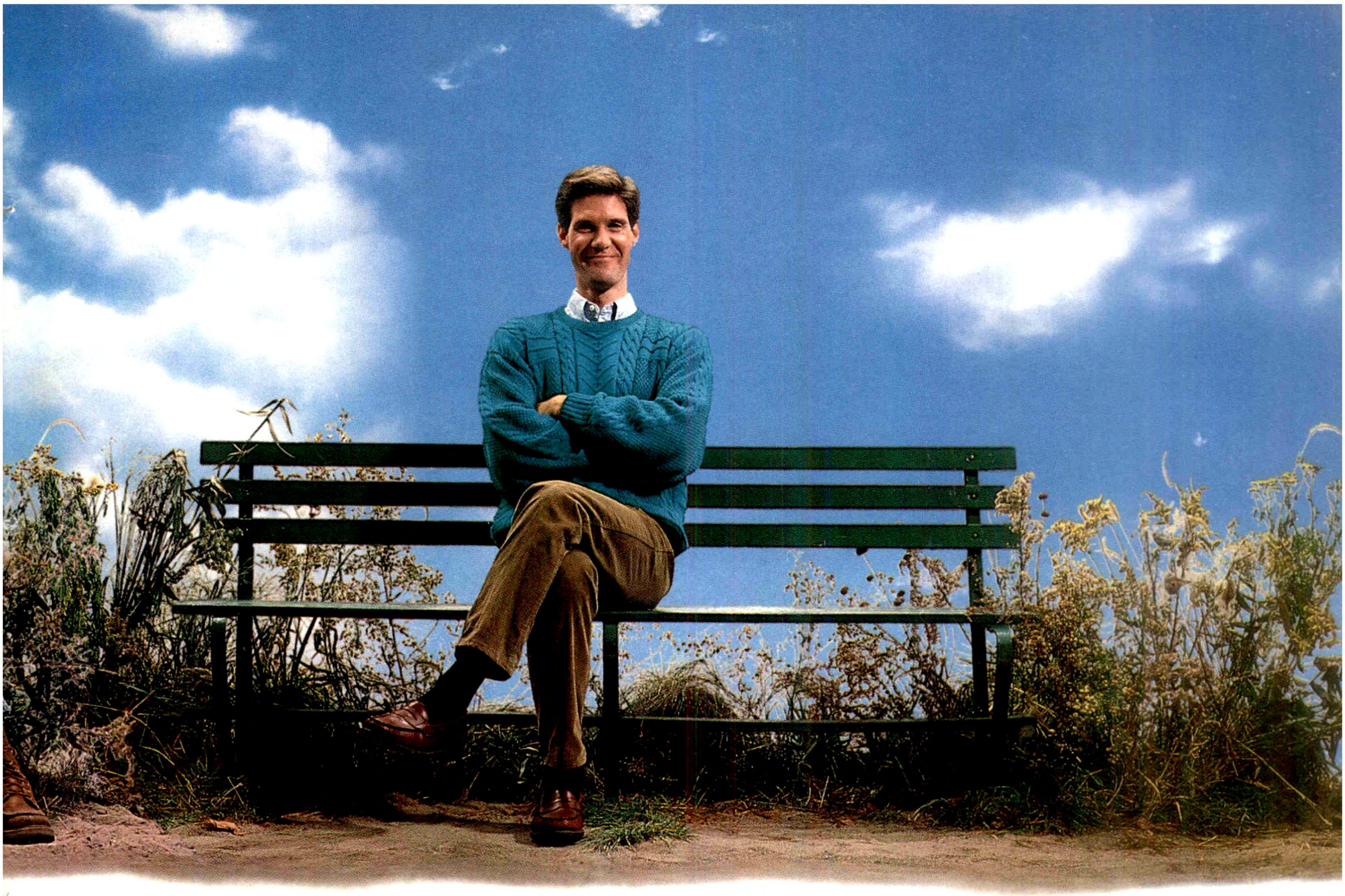

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BRIEF SUMMARY

Beconase AQ® Nasal Spray, 0.042%*
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SHAKE WELL BEFORE USE.

The following is a brief summary only. Before prescribing, see complete prescribing information in Beconase® Inhalation Aerosol and Beconase AQ® Nasal Spray product labeling.

CONTRAINDICATIONS: Hypersensitivity to any of the ingredients of either preparation contraindicates its use.

WARNINGS: The replacement of a systemic corticosteroid with Beconase® Inhalation Aerosol or Beconase AQ® Nasal Spray can be accompanied by signs of adrenal insufficiency.

Careful attention must be given when patients previously treated for prolonged periods with systemic corticosteroids are transferred to Beconase Inhalation Aerosol or Beconase AQ Nasal Spray. This is particularly important in those patients who have associated asthma or other clinical conditions where too rapid a decrease in systemic corticosteroids may cause a severe exacerbation of their symptoms.

Studies have shown that the combined administration of alternate-day prednisone systemic treatment and orally inhaled beclomethasone increases the likelihood of hypothalamic-pituitary-adrenal (HPA) suppression compared to a therapeutic dose of either one alone. Therefore, Beconase Inhalation Aerosol and Beconase AQ Nasal Spray treatment should be used with caution in patients already on alternate-day prednisone regimens for any disease.

If recommended doses of intranasal beclomethasone are exceeded or if individuals are particularly sensitive or predisposed by virtue of recent systemic steroid therapy, symptoms of hypercorticism may occur, including very rare cases of menstrual irregularities, acneiform lesions, and cushingoid features. If such changes occur, Beconase Inhalation Aerosol and Beconase AQ Nasal Spray should be discontinued slowly consistent with accepted procedures for discontinuing oral steroid therapy.

PRECAUTIONS: General: During withdrawal from oral steroids, some patients may experience symptoms of withdrawal, eg, joint and/or muscular pain, lassitude, and depression.

Rarely, immediate hypersensitivity reactions may occur after the intranasal administration of beclomethasone.

Extremely rare instances of wheezing, nasal septum perforation, and increased intraocular pressure have been reported following the intranasal application of aerosolized corticosteroids. Although these have not been observed in clinical trials with Beconase AQ® Nasal Spray, vigilance should be maintained.

In clinical studies with beclomethasone dipropionate administered intranasally, the development of localized infections of the nose and pharynx with *Candida albicans* has occurred only rarely. When such an infection develops, it may require treatment with appropriate local therapy or discontinuation of treatment with Beconase® Inhalation Aerosol or Beconase AQ Nasal Spray.

If persistent nasopharyngeal irritation occurs, it may be an indication for stopping Beconase AQ Nasal Spray.

Beclomethasone dipropionate is absorbed into the circulation. Use of excessive doses of Beconase Inhalation Aerosol or Beconase AQ Nasal Spray may suppress HPA function.

Beconase Inhalation Aerosol and Beconase AQ Nasal Spray should be used with caution, if at all, in patients with active or quiescent tuberculous infections of the respiratory tract; untreated fungal, bacterial, or systemic viral infections; or ocular herpes simplex.

For either preparation to be effective in the treatment of nasal polyps, the aerosol or spray must be able to enter the nose. Therefore, treatment of nasal polyps with these preparations should be considered adjunctive therapy to surgical removal and/or the use of other medications that will permit effective penetration of these preparations into the nose. Nasal polyps may recur after any form of treatment.

As with any long-term treatment, patients using Beconase Inhalation Aerosol or Beconase AQ Nasal Spray over several months or longer should be examined periodically for possible changes in the nasal mucosa.

Because of the inhibitory effect of corticosteroids on wound healing, patients who have experienced recent nasal septal ulcers, nasal surgery, or trauma should not use a nasal corticosteroid until healing has occurred.

Although systemic effects have been minimal with recommended doses, this potential increases with excessive doses. Therefore, larger than recommended doses of Beconase Inhalation Aerosol and Beconase AQ Nasal Spray should be avoided.

Information for Patients: Patients being treated with Beconase Inhalation Aerosol or Beconase AQ Nasal Spray should receive the following information and instructions. This information is intended to aid in the safe and effective use of medication. It is not a disclosure of all possible adverse or intended effects. Patients should use these preparations at regular intervals since their effectiveness depends on their regular use. The patient should take the medication as directed. It is not acutely effective, and the prescribed dosage should not be increased. Instead, nasal vasoconstrictors or oral antihistamines may be needed until the effects of Beconase Inhalation Aerosol or Beconase AQ® (beclomethasone dipropionate, monohydrate) Nasal Spray are fully manifested. One to two weeks may pass before full relief is obtained. The patient should contact the doctor if symptoms do not improve, or if the condition worsens, or if sneezing or nasal irritation occurs. For the proper use of either unit and to attain maximum improvement, the patient should read and follow carefully the patient's instructions section of the package insert.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Treatment of rats for a total of 95 weeks, 13 weeks by inhalation and 82 weeks by the oral route, resulted in no evidence of carcinogenic activity. Mutagenic studies have not been performed.

Impairment of fertility, as evidenced by inhibition of the estrous cycle in dogs, was observed following treatment by the oral route. No inhibition of the estrous cycle in dogs was seen following treatment with beclomethasone dipropionate by the inhalation route.

Pregnancy: ***Teratogenic Effects: Pregnancy Category C:*** Like other corticoids, parenteral (subcutaneous) beclomethasone dipropionate has been shown to be teratogenic and embryocidal in the mouse and rabbit when given in doses approximately ten times the human dose. In these studies, beclomethasone was found to produce fetal resorption, cleft palate, agnathia, microstomia, absence of tongue, delayed ossification, and agenesis of the thymus. No teratogenic or embryocidal effects have been seen in the rat when beclomethasone dipropionate was administered by inhalation at ten times the human dose or orally at 1,000 times the human dose. There are no adequate and well-controlled studies in pregnant women. Beclomethasone dipropionate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully observed.

Nursing Mothers: It is not known whether beclomethasone dipropionate is excreted in human milk. Because other corticosteroids are excreted in human milk, caution should be exercised when Beconase (beclomethasone dipropionate, USP) Inhalation Aerosol or Beconase AQ Nasal Spray is administered to nursing women.

Pediatric Use: Safety and effectiveness in children below 6 years of age have not been established.

ADVERSE REACTIONS: In general, side effects in clinical studies with both preparations have been primarily associated with irritation of the nasal mucous membranes.

Extremely rare instances of wheezing, nasal septum perforation, and increased intraocular pressure have been reported following the intranasal administration of aerosolized corticosteroids (see PRECAUTIONS).

Rare cases of immediate and delayed hypersensitivity reactions, including urticaria, angioedema, rash, and bronchospasm, have been reported following the oral and intranasal inhalation and administration of beclomethasone.

Beconase® Inhalation Aerosol: Adverse reactions reported in controlled clinical trials and long-term open studies are described below. Sensations of irritation and burning in the nose (11 per 100 patients) following the use of Beconase Inhalation Aerosol have been reported. Also, occasional sneezing attacks (10 per 100 adult patients) have occurred immediately following the use of the intranasal inhaler. This symptom may be more common in children. Rhinorrhea may occur occasionally (1 per 100 patients).

Localized infections of the nose and pharynx with *C albicans* have occurred rarely (see PRECAUTIONS).

Transient episodes of epistaxis have been reported in 2 per 100 patients. Ulceration of the nasal mucosa has been reported rarely.

Systemic corticosteroid side effects were not reported during controlled clinical trials. If recommended doses are exceeded, however, or if individuals are particularly sensitive, symptoms of hypercorticism, ie, Cushing's syndrome, could occur.

Beconase AQ® Nasal Spray: Adverse reactions reported in controlled clinical trials and open studies are described below.

Mild nasopharyngeal irritation has been reported in up to 24% of patients treated, including occasional sneezing attacks (about 4%) occurring immediately following use of the spray. In patients experiencing these symptoms, none had to discontinue treatment. The incidence of transient irritation and sneezing was approximately the same in the group of patients who received placebo in these studies, implying that these complaints may be related to vehicle components of the formulation.

Fewer than 5 per 100 patients reported headache, nausea, or lightheadedness. Fewer than 3 per 100 patients reported nasal stuffiness, nosebleeds, rhinorrhea, or tearing eyes.

OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information. RB2-1006 March 1989

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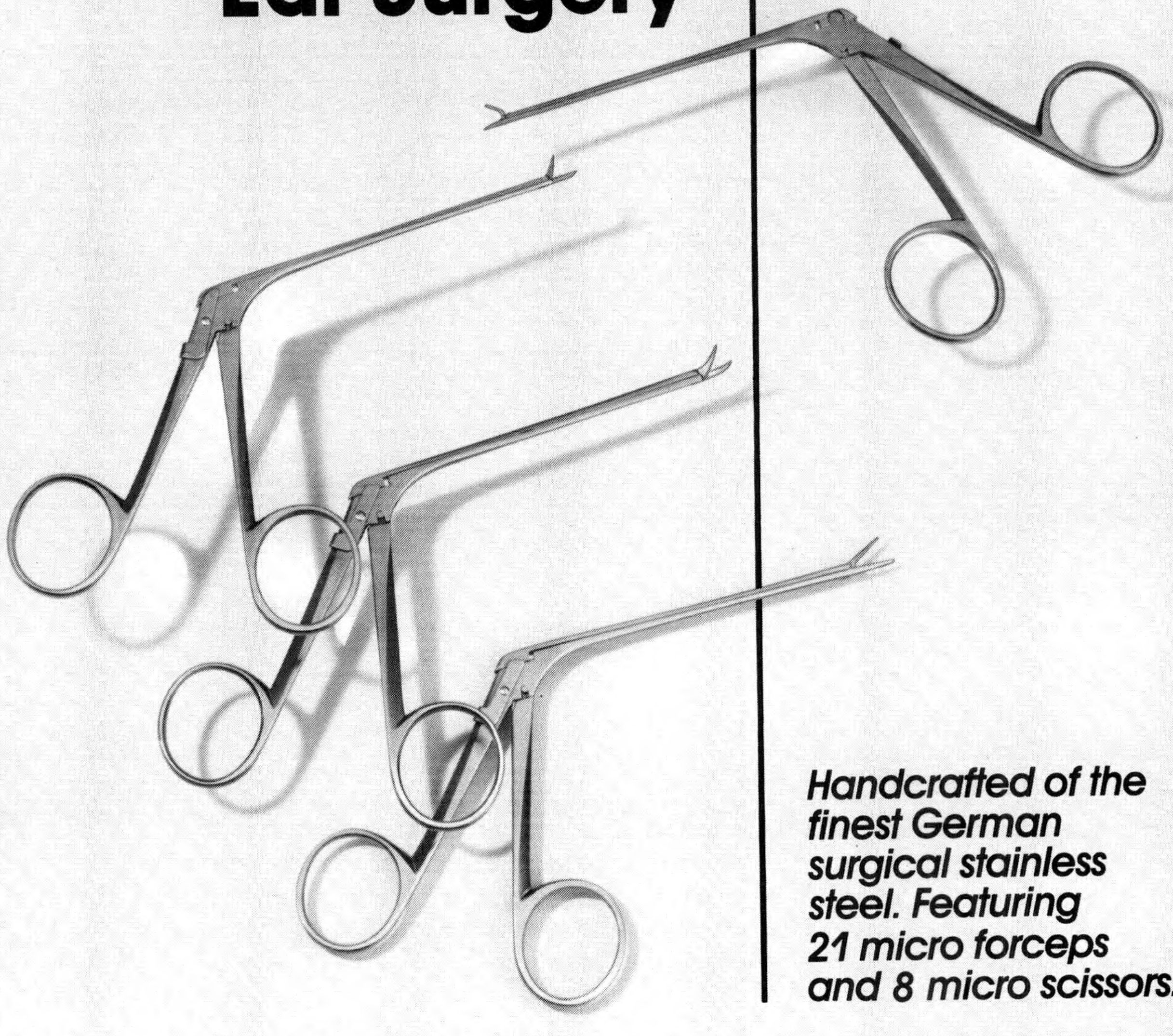

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Printed on acid-free paper

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Ann Otol Rhinol Laryngol 99:1990

EARLY SUPRAGLOTTIC CANCER

LAWRENCE W. DESANTO, MD

SCOTTSDALE, ARIZONA

Early supraglottic cancers (T1 and T2) are treated today with several dissimilar programs. Operation or irradiation alone, combined irradiation and operation, and irradiation with operation for salvage are the options. This study analyzed the effectiveness of operation alone in a group of 94 patients with early lesions. There were no local failures in the group. The only cause of failure was recurrence in the neck and distant metastasis in 15% of patients. Comparisons were made of effectiveness of treatment with regard to local and neck failure, voices retained, frequency of retreatment, and determinate survival to the alternate treatment programs. No differences were found in regard to survival with any of the contemporary programs. There are differences in terms of retreatment frequency, voice preservation, and cause of failure between programs. Conservation surgery is preserving voices today. Combined therapy seems of little value in the early cancers.

KEY WORDS — conservation surgery, early cancer, supraglottic cancer.

INTRODUCTION

Early supraglottic cancers are those of the epiglottis or epiglottis and laryngeal surface of the arytenoepiglottic folds that have not extended to cordal fixation or onto the tongue base. They are primary growths that may be stage I or II depending on whether they have metastasized to the neck. The oncologic issues are different from those of early glottic cancer. T2 supraglottic cancer can have a tumor volume in the preepiglottic space that will exceed that of a similarly staged glottic cancer.[1] These tumors metastasize to the lateral neck, and both sides of the neck are at risk to some degree in all but the earliest lesions.[2,3]

As with all early squamous cell cancers, there is no consensus on treatment. Single-modality therapy using operation alone or irradiation alone appeals to some. Others think that combined sequential therapy with irradiation before or after operation is important.[4,5]

The management of the primary tumor has evolved over the last few decades. Laryngectomy has yielded to acceptance of supraglottic resection. Extensions and modifications of the conservation operations have provided flexibility and relative safety for some patients.

Issues concerning the neck are more lucid today. Both sides of the neck seem to be at risk and neck failure is recognized as a major problem. Neck dissection is seen as an imperfect solution for neck metastasis. The solutions to these neck problems are less obvious.

The purpose of this study was to evaluate the success of primary surgical treatment to the primary and the neck in early supraglottic cancer (T1 and T2) and to compare single-modality surgical treatment to multimodality combined therapy.

MATERIAL AND METHODS

Between Jan 1, 1974, and Dec 31, 1983, there were 94 patients treated for pathologic stage I (29) and pathologic stage II (65) supraglottic cancer by the staff and residents of the Department of Otolaryngology–Head and Neck Surgery of the Mayo Clinic in Rochester, Minn. There were 17 women and 77 men (mean age, 59 years; range, 31 to 87 years; 53% >60 years).

Follow-up data were available on all patients. Each was followed until death for those who died or until July 1988 for those who were alive. Mean length of follow-up was 7.4 years and the minimum follow-up was 4.5 years.

Treatment. All patients were treated by operation alone as their definitive therapy. There were seven patients who were treated again by operation after irradiation failure.

Nine patients received irradiation to the neck after recurrence within the treated side of the neck. No patient received combined operation and irradiation as planned combined therapy.

Type of Surgical Treatment. Figure 1 shows the type of surgical treatment by primary stage. Seventy of the 94 patients (74%) had some type of voice-preserving procedure. Twenty-four patients (26%) underwent laryngectomy for either surgical salvage of irradiation failure (7) or advanced age and poor pulmonary function (17). All but 3 patients with a T1 primary cancer had some form of conservation operation. Table 1 shows the neck treatments.

Pathologic Stage of Neck. Figure 2 shows the pathologic stage of the neck (node-positive or node-negative) by primary stage. Whereas only 20% of the pathologic stage I primary patients had metastasis to one side of the neck, 43% of patients with

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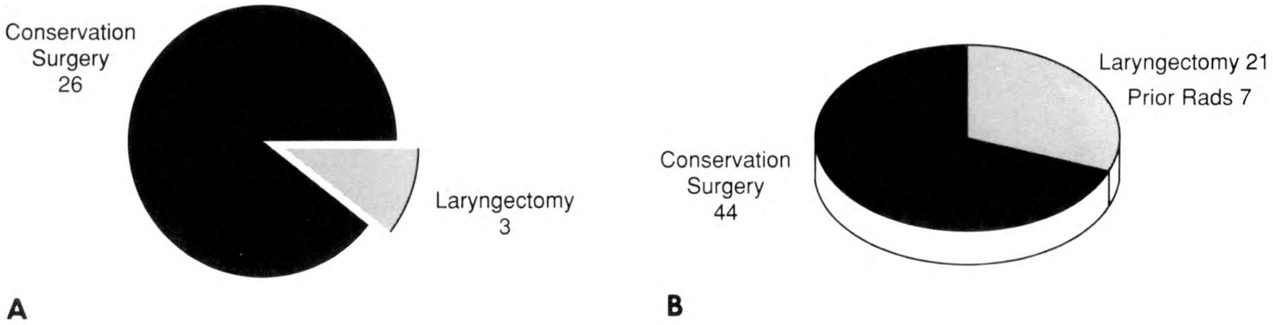

Fig 1. Types of operation for early supraglottic cancer. A) Stage T1. B) Stage T2.

pathologic stage II primary disease had proven metastasis to one or both sides of the neck at the time of primary treatment.

RESULTS

Figure 3 summarizes the results of treatment by pathologic T stage. Sixty-nine patients (73%) were alive at the time of data analysis. Eleven patients (12%) died of something other than cancer. Of these, 1 died in the first year, 1 in each of the second, third, and fourth years after cancer treatment, and the other 7 died after 5 years. Thus, 85% of this group of patients were either alive after treatment or dead of some cause other than larynx cancer during the follow-up period. There was one treatment death.

Results of Primary Treatment. No patient died of primary treatment failure and no primary recurrences were detected. No patient had any secondary treatment to the primary site.

Results of Neck Treatment. Of the 62 patients who had unilateral dissection at the time of primary treatment, 22 of their dissected sides of the neck contained metastatic cancer. Seven of these patients died of cancer (Fig 4). Of the 40 patients for whom the dissected side of the neck was negative for metastasis, none died of cancer. Delayed metastasis on the second side of the neck developed in 5 patients. Each of them had positive nodes on the initially dissected side, but they were clinically negative at the time of primary treatment on the other side. Three of the 5 patients died of cancer.

Twelve patients underwent bilateral simultaneous dissection at the time of primary treatment. Ten of these remained free of cancer until follow-up or death from other causes and two died from distant metastasis.

Twenty patients had no dissection at the time of the primary treatment. Seven of these were thought later to have palpable neck disease and were given a delayed unilateral dissection. None of these patients were proven to have pathologic neck metastasis in the delayed neck dissection specimen. One node-negative patient died from distant metastasis without neck recurrence.

DISCUSSION

There are several ways to compare the success of the various treatment schemes used today for early supraglottic cancer. Operation alone, irradiation alone, radical irradiation with operation for salvage, and combined irradiation and operation are all options. The first and most important measure of success is determinate survival (the probability of getting well and staying well after cancer treatment); others include primary control with the first treatment, neck control, and percentage of patients with glottic voices. Table 2[4-9] attempts to make these comparisons by using the most recent studies of early supraglottic cancer, including this study.

The probability of being alive without cancer after factoring out death from other causes ranges from 84% in a program of irradiation for cure with operation for salvage cited by Levendag et al[6,7] to 96% in the report by Weems et al,[4] in which nearly half the patients were excluded because of death from other causes in a program that included both irradiation with operation for salvage and planned combined therapy. There was no significant difference as a function of the treatment program.

One of the open issues in the treatment of supraglottic cancer is the value of and the decision to use combined therapy. Shimm and Coulthard[10] reported 5-year survival in 40 patients with T1 and T2 supraglottic cancers of 60% and 53%, respectively, in tumors treated with operation followed by irradiation. The control of the primary tumor was cited as 93%. The University of Florida experience with operation plus adjuvant irradiation was about the same (94%) for T1 and T2 lesions, but only 39% of patients retained a lung-powered glottic voice.[4] Spaulding et al,[5] from the Medical College

TABLE 1. TREATMENT FOR STAGES T1 AND T2 SUPRAGLOTTIC CANCER

Treatment		Patients No.	Patients %
No neck dissection		11	12
Unilateral dissection		62	66
Bilateral dissection		21	22
Simultaneous	12		
Delayed	9		

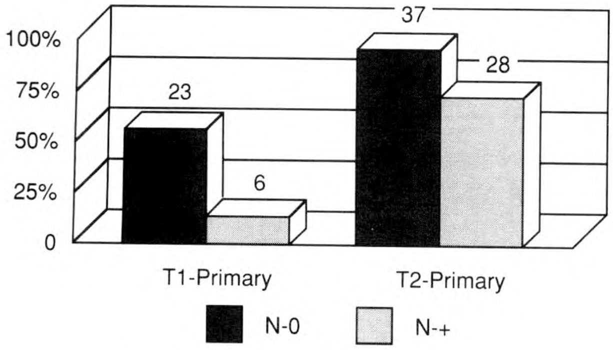

Fig 2. Neck stage by pathologic stage.

of Virginia, reported on 33 patients treated by conservation operation followed by irradiation. The 2-year "adjusted" survival that excluded death from other causes was 97% and at 3 years it was 89%. Series that report patients treated by irradiation for cure and operation reserved for salvage have about the same determinate survival.[8,11,12] In none of these comparisons is there a compelling case for multimodality therapy, as there is no significant incremental difference between those patients treated with operation alone and those treated with operation and irradiation. With irradiation for cure and operation for salvage, the number of preserved voices is about one third less than in the surgically treated patients. That there is so little difference in results in terms of death from cancer with any treatment scheme should not be too surprising. Only about 15 of 100 patients die of cancer, regardless of the treatment. With an expected higher frequency of death from other causes because of age and because patients with cancer die at a faster rate from other causes than those without cancer, there is not much room for improvement. If one considers morbidity and mortality from any extra treatment, it may be that whatever potential for improvement there might be with multimodality therapy is negated by death from the extra treatment. An alternative conclusion is that there is no benefit from combined therapy.

There is general agreement that control of the primary in surgically treated early supraglottic cancer is not a serious problem. This study and two previous reviews of supraglottic cancers[2,3] confirmed that impression. There are data from other centers that document the high probability of control of the primary disease by operation alone or combined therapy.[6,7,13] There are no compelling data to suggest that primary control alone justifies multimodality therapy, because there are so few local recurrences in surgically treated disease.

That failure to control neck metastasis is the problem is not contested. The Memorial Sloan-Kettering experience[7] involved 29% neck relapse (23 of 79 patients) in surgically treated early supraglottic cancer. The neck relapse rate in that report was equal in patients with dissected necks and in those whose necks were not treated: 9 of 31 patients who had elective neck dissection in clinically negative necks had a relapse in the neck. All of their cancer deaths were in the patients who had neck recurrence in the dissected side or who had delayed neck metastasis. The impact of delayed metastasis and neck recurrence is confirmed by this study. Any neck recurrence after the primary was treated was serious and usually fatal. This study had 13 neck recurrences after neck dissection — 5 contralateral and 8 in a dissected neck — with only 2 survivors (Fig 4).

The problems of neck recurrence are obvious. What to do to avoid this serious problem is less certain. The options are limited. One can dissect both sides of the neck in all patients, one can irradiate both sides of the neck in all patients, or one can do nothing to the clinically negative sides of the neck and then watch and wait and perform delayed dissections on those that may need them. The third course is risky. When disease becomes apparent it is either too late or the results are compromised. To irradiate bilaterally or to dissect bilaterally all patients' necks means that at least two thirds of them are treated excessively and derive no benefit. These are the two thirds who do not have neck metastasis.

An imperfect compromise seems possible in surgically treated patients. That compromise is to do a unilateral dissection that is for staging if it is negative. If it is positive, then the dissection is partially therapeutic. The staging value of dissection is veri-

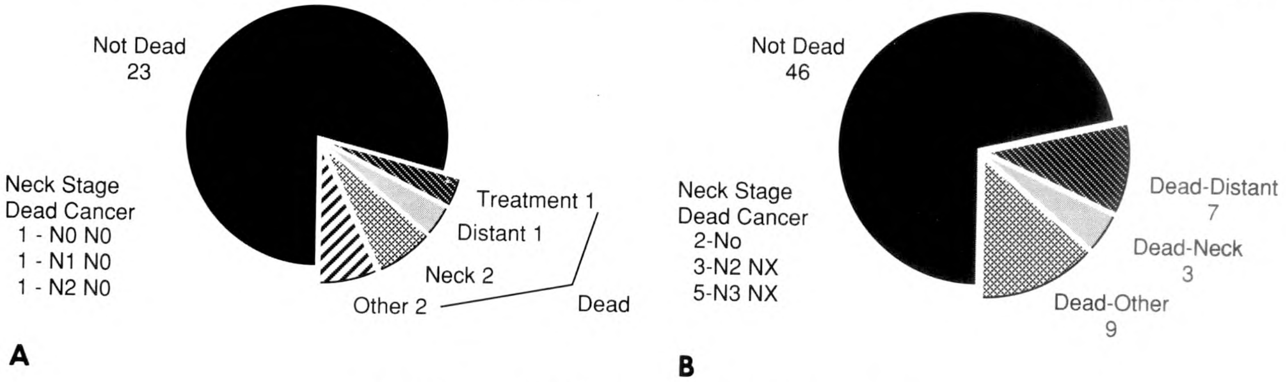

Fig 3. Status at last follow-up. A) Stage T1. B) Stage T2.

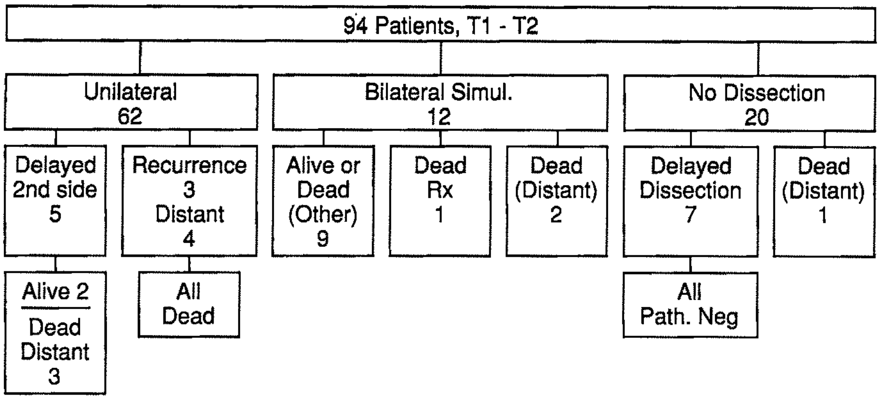

Fig 4. Results of neck treatment.

fied by the observation that no patient who had a negative dissection had delayed unilateral or contralateral metastasis in this study. In a larger study of all primary stages of supraglottic cancer we found only one delayed contralateral metastasis in 98 patients who had unilateral negative dissection, whereas in over one third of those with a positive dissection on one side, delayed contralateral metastasis developed.[14] The staging value of a negative dissection limits extra therapy to only those patients for whom there might be some benefit. The population at greatest risk can be treated by a second-side neck dissection or irradiation and the rest can be spared extra treatment.

The simplest option is to do a second-side dissection on those patients in whom metastasis is found in the first side. This course implies bilateral simultaneous dissections in some patients. What we will do now is a staging unilateral dissection on whatever side seems most promising on the basis of palpation and a careful study of the primary. In many instances there is no compelling reason to pick one side of the neck to dissect over the other. The choice then is a random event. If the first dissected side is pathologically positive (this information must be obtained while operating on the primary), then the second side of the neck is dissected. If the first side is negative, nothing is done to the second side. For those who believe that irradiation of the clinically negative side of the neck is of the same value as a neck dissection, the same data can be used to select those who will have elective neck irradiation. This is then a combined therapy program with extra problems, time, and costs.

It is important to remember that those patients who do not have cancer in the second side of the neck derive no benefit from either a dissection or irradiation. Most patients do not have metastasis on the contralateral side of the neck.

CONCLUSIONS

The treatment of early supraglottic cancer is not settled. Some look to single-modality treatment, others use some form of combined therapy, and still others use a managed program of irradiation for cure and operation for salvage. Regardless of the treatment scheme used, all the results at 3 or 5 years cluster around 85%. With survival statistics as good as these it is unlikely that any scheme that uses what we have available today is going to make much more of an impact. It may well be that the idea of "biologic determinism" is valid. Any logical single or sequential treatment will help those who have whatever is immunologically necessary to get well, and those who do not have it will not. About 15% of patients will die in spite of the treatment.

Any questions about local control seem settled. Treatment programs that include operation for the primary, either alone or in combination with irradiation, are successful. There does not seem to be any compelling reason concerning the primary alone to encourage more treatment than operation alone.

Irradiation alone is about 30% less effective for

TABLE 2. SURVEY OF STUDIES OF EARLY SUPRAGLOTTIC CANCER

Author	*Treatment*	*No. of Patients*	*Determinant Survival >3 yr (%)*	*Glottic Voice (%)*	*Local Control 1st Rx (%)*	*Neck Control (%)*	*Retreatment (%)*
Spaulding et al[5]	Combined	20	89	90	96	90	
Levendag and Vikram[6]	RRSS	96	84	67	60	74	
Levendag et al[7]	Operation alone	79	85	39*	97	71	
Spaulding et al[8]	RRSS	33	85	65	65	N/A	56
Lee and Goepfort[9]	Combined	34	87	N/A	100	95	
DeSanto (present study)	Operation alone	94	85	74	100	87	13
Weems et al[4]	RRSS and combined	83	96	72	84	N/A	34†

RRSS — radical irradiation with surgical salvage, Rx — treatment.
*Before supraglottic resection used.
†Includes neck dissection in irradiated patients.

primary control. Some of the patients who fail irradiation can be salvaged, usually by laryngectomy. When laryngectomy was the only surgical option, the voice-sparing potential of irradiation for cure and operation for salvage was attractive, but that time is over. Modern conservation surgery saves more voices. The frequency with which a lung-powered voice can be preserved is changing.

The unsettled issue remains control of the neck. The idea that one can combine the best features of operation (ie, local control) with the presumed value of postoperative irradiation to the neck is attractive. The numbers are less convincing.

Management of neck metastasis remains the unsolved problem in early supraglottic cancer. Whether neck metastasis can be controlled may relate more to what the patient brings to treatment than to what we do at treatment.

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Ann Otol Rhinol Laryngol 99:1990

TRANSCUTANEOUS INTRAFOLD INJECTION FOR UNILATERAL VOCAL FOLD PARALYSIS: FUNCTIONAL RESULTS

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This paper presents the technique of transcutaneous intrafold silicone injection and the functional results of 44 procedures in 42 patients. The injection is given under local anesthesia with the patient in a supine position. The needle is inserted through the cricothyroid space. The location of the needle as well as the effect of injection is monitored by means of a fiberscope connected to a television camera and screen. The preoperative and postoperative vocal function was multidimensionally evaluated with the use of a test battery consisting of the maximum phonation time (MPT), mean airflow rate (MFRc), fundamental frequency (F0) range and sound pressure level (SPL) range of phonation, pitch perturbation quotient (PPQ), amplitude perturbation quotient (APQ), and normalized noise energy (NNEa). In the majority of the patients, MPT, F0 range, and SPL range increased and MFRc, PPQ, APQ, and NNEa decreased postoperatively. In the overall evaluation based on the test values of these parameters, the result was excellent for 16 procedures, good for 16, fair for 7, and poor for 5. The most frequent cause of failure was an insufficient amount injected.

KEY WORDS — functional results, intrafold injection, transcutaneous approach, vocal fold paralysis.

Many surgical techniques have been successfully employed worldwide in treating glottic incompetence caused by unilateral vocal fold paralysis. They can be classified into three major categories: medialization surgery, intrafold injection, and neuromuscular surgery. Techniques of medialization surgery can be further classified into three major groups: surgical augmentation, medial shift of the thyroid cartilage, and rotation of the arytenoid cartilage. Intrafold injection can be performed transorally by use of a direct laryngoscope or an indirect laryngeal mirror, or transcutaneously through the cricothyroid space.[1]

The senior author (M.H.) of this paper was trained first with the surgical augmentation technique in 1959. Since then, we have employed several techniques, including surgical augmentation, medial shift of the thyroid cartilage, and transoral and transcutaneous intrafold injections. Since 1983, because of its technical simplicity, minimum surgical invasion, and wide applicability, transcutaneous injection has been the first choice in our institution for nearly all patients with unilateral vocal fold paralysis who require surgical treatment. A preliminary report of this procedure was given in 1985.[2] The purposes of this paper are to describe the technique in detail and to report objective functional results in a series of patients.

METHODS AND SUBJECTS

Injection Technique. We employ Phycon 6500 and Phycon 6500 Additive medical silicone rubber (Fuji Industrial Co, Tokyo, Japan), which was first used for intrafold injection by Fukuda.[3] Phycon 6500 has a viscosity of 10,000 centistokes and Phycon 6500 Additive, a viscosity of 100 centistokes. Prior to injection, they are mixed in the ratio of 1:2 to 1:3, and then a few drops of catalyzer are added for the purpose of solidification. It takes 10 to 15 minutes for Phycon to solidify following the addition of the catalyzer. Injection should be completed before Phycon is solidified.

Following local anesthesia of the nasal, pharyngeal, and laryngeal mucosa, the patient assumes a supine position with the anterior neck stretched. A fiberscope is inserted into the larynx via the nose and the fiberscopic laryngeal image is viewed on a television screen throughout the procedure. The entire procedure is also documented on videotape.

Injection is given with a 2-mL locking syringe and a dental needle. Hypodermic anesthesia is performed at the injection site. The location of the vocal fold is estimated as shown in Fig 1.

The vocal fold edge is usually positioned horizontally at the midlevel of the anterior angle of the thyroid cartilage. The tip of the vocal process of the arytenoid cartilage is located approximately at the anteroposterior midpoint of the thyroid lamina. The membranous vocal fold is, therefore, located in the anteroinferior quadrant of the thyroid lamina. In order to facilitate a correct placement of the injection needle, it is advisable to mark the estimated location of the vocal fold edge and that of the vocal process on the cervical skin, as well as the location of the upper, lower, and posterior edges of the thyroid cartilage; the upper and lower edges of the cricoid arch; and the midline (Fig 2A). The depth of needle insertion is also estimated prior to insertion (Fig 2B).

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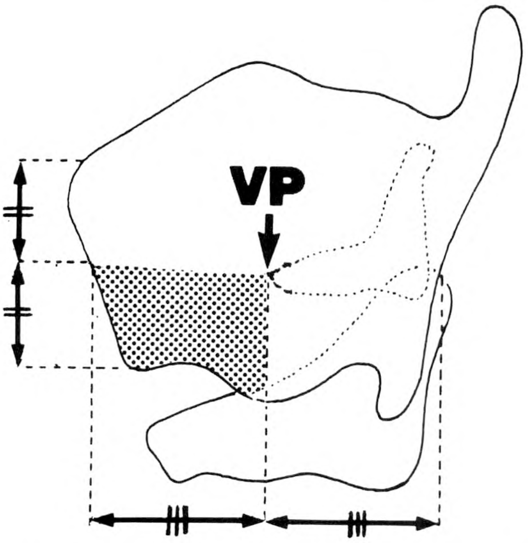

Fig 1. Estimation of location of tip of vocal process (VP) and vocal fold (dotted area).

The needle is inserted at the level of the upper edge of the cricoid arch, approximately 5 mm from the midline on the paralyzed side. It is directed posteriorly, superiorly, and laterally between the thyroid and cricoid cartilages. In order to monitor its location, the needle is gently shaken medially back and forth as it proceeds. When small movements are observed in the region lateral and slightly anterior to the tip of the vocal process, the injection is started. The bevel of the needle must be directed laterally so that the silicone rubber does not enter the mucosa. Once the silicone rubber enters the mucosa, the mucosa becomes stiff and, consequently, disturbances of vocal fold vibration and dysphonia may result. Injection is performed slowly and carefully with visual and auditory monitoring.

Figure 3 shows laryngeal images of a patient before and after injection.

Subjects. During the period from July 1983 to April 1989, a total of 51 patients, 30 males and 21 females, underwent transcutaneous intrafold injection for unilateral vocal fold paralysis. Their ages ranged from 17 to 81 years, with a mean age of 56.7 years. The cause of paralysis was thyroid cancer or its surgical treatment in 11 cases, esophageal cancer or its surgical treatment in 10, lung cancer or its surgical treatment in 8, aortic aneurysm or its surgical treatment in 4, a heart operation in 1, vertebral operations in 2, operation on the neck in 1, neck trauma in 1, and neuritis in 13. Two patients underwent two procedures because the first was not very successful. The preoperative and postoperative vocal function was evaluated for 44 procedures in 42 patients. The other 9 patients did not come back for postoperative evaluation. This paper describes the functional results of the 44 procedures.

Evaluation of Vocal Function. The vocal function was evaluated by means of seven measures: maximum phonation time (MPT), mean airflow rate during phonation over comfortable duration (MFRc), fundamental frequency (F_0) range of phonation, sound pressure level (SPL) range of phonation, pitch perturbation quotient (PPQ), amplitude perturbation quotient (APQ), and normalized noise energy for the frequency band 0 to 4 kHz (NNEa). The first two reflect the degree of glottic incompetence, the following two roughly show the ability of F_0 and SPL control, and the last three reflect some important aspects of voice quality.

The postoperative evaluation was conducted 1 to 1,701 days following injection. Evaluation was repeated on different occasions in some patients. It was impossible to evaluate the vocal function at the same given interval after injection in all subjects. Figure 4 depicts temporal changes of MFRc and PPQ following injection. There were no consistent and systematic changes in MFRc and PPQ that depended on the interval following injection. This was also the case with the other five test items. Therefore, the most recent test values for each procedure were employed in the following data analyses.

For each test, scores were assigned according to the following rules. When the postoperative value

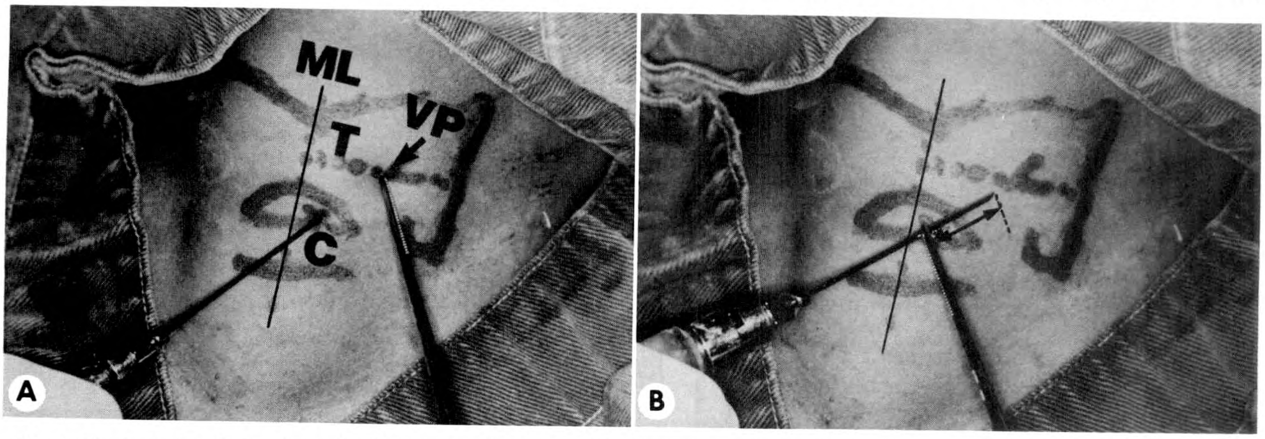

Fig 2. Photographs of anterior neck. A) Estimated location of tip of vocal process (VP). T — thyroid cartilage, C — cricoid cartilage, ML — midline. B) Estimated depth (arrow) of needle insertion.

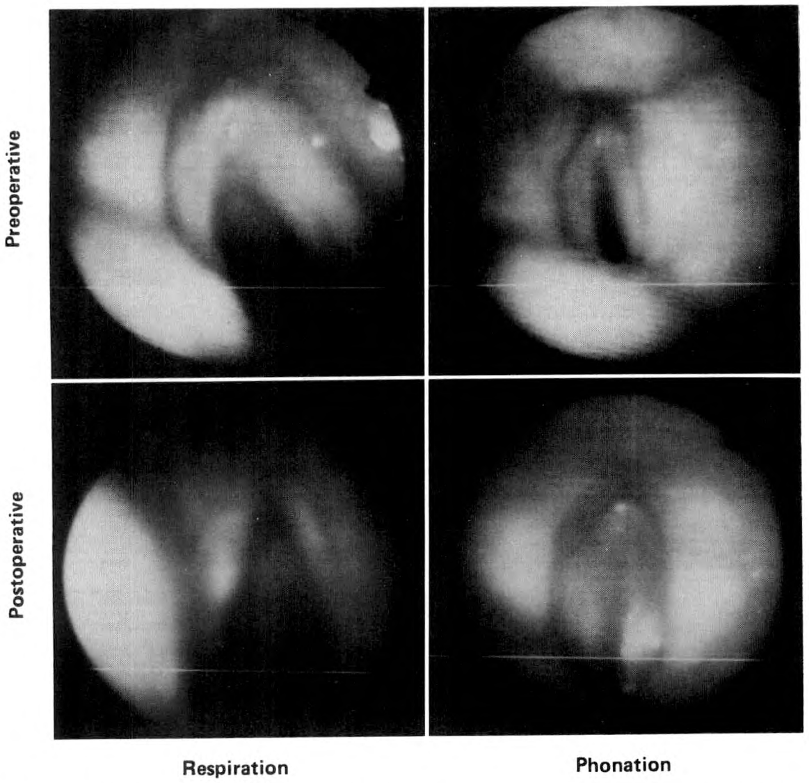

Fig 3. Preoperative and postoperative laryngeal images. Note that bowing of vocal fold edge and glottic incompetence are eliminated postoperatively.

was within normal range, a score of 2 was assigned. When the test value was improved postoperatively but remained out of normal range, a score of 1 was assigned. A score of 0 was assigned when injection caused no change, and a score of −1 was assigned when the test value was worsened. An overall evaluation was made in the following way. When the sum of the scores for the seven tests was 11 to 14, the result was categorized as excellent. A sum of 6 to 10 was categorized good; 1 to 5, fair; and 0 or less, poor. For five injection procedures, data for F0 range and SPL range were not available, whereas data for all seven tests were obtained for the other 39 procedures. In the former five cases, a sum of the scores of 8 to 10 was categorized excellent; 4 to 7, good; 1 to 3, fair; and 0 or less, poor.

Computed Tomography. In order to determine whether or not the injected silicone rubber had stayed in place, computed tomography was conducted on nine patients 63 to 2,156 days after injection.

Review of Injection Procedure. The entire injection procedure for each patient documented on videotape was repeatedly reviewed and the adequacy of each procedure was evaluated.

RESULTS

Score for Each Test. Figure 5 depicts scatterplots of the preoperative and postoperative values of each test, and the Table shows a summary of the results. The majority of the procedures resulted in an improvement for each test, ie, an increase in MPT, F0 range, and SPL range and a decrease in MFRc, PPQ, APQ, and NNEa. The occurrence of scores of 2 and 1 was most frequent for MPT (89%), second most frequent for MFRc (84%), and least frequent for F0 range (69%). In other words, the effect of intrafold injection was manifested most frequently in an improvement of glottic closure and least frequently in the ability of F0 control. The F0 range was reduced in 10, or 26%, of the 39 procedures evaluated.

Overall Evaluation. The result of the overall evaluation was excellent for 16 procedures, good for 16, fair for 7, and poor for 5.

Analyses of Failures. Among the five procedures with a poor result, the amount of injection was insufficient in three and too much in one procedure. One of the three patients in whom the amount of injection was insufficient underwent another injection later under a direct laryngoscope with an excellent result. The other two were not motivated to have an additional procedure. In the fifth case, the injection was conducted adequately. This patient, however, had a deep sulcus on the affected vocal fold and she developed strained phonation. Both MPT and MFRc were within normal range postoperatively, but PPQ, APQ, and NNEa were increased, reflecting an unfavorable voice quality.

Among the seven procedures with a fair result, the amount of injection was not enough in five procedures. Two of the five patients received another transcutaneous injection later with a successful result. In the other three patients, the cause of paralysis had been lung cancer, an operation for lung can-

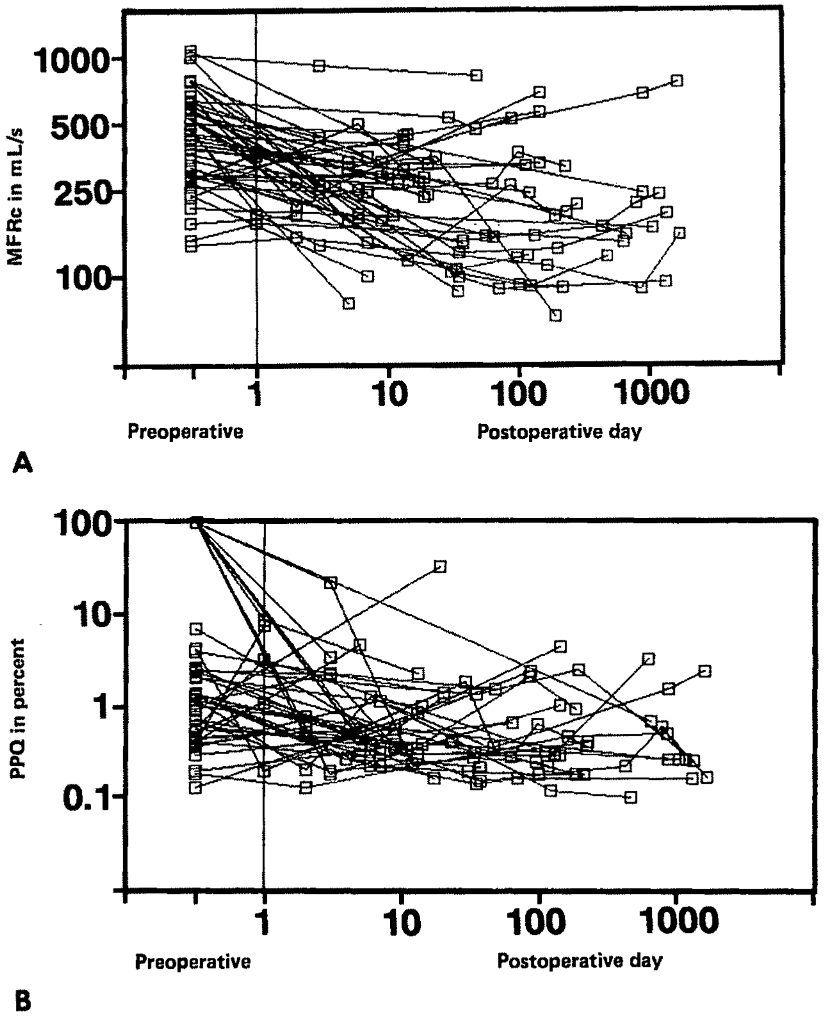

Fig 4. Temporal changes of A) mean airflow rate during phonation over comfortable duration (MFRc) and B) pitch perturbation quotient (PPQ) following intrafold injection.

cer, and an operation for esophageal cancer, respectively. They were more or less happy with the slight improvement in voice and did not want to have another injection for a possible further improvement. The sixth patient presented with some improvement of MPT, MFRc, PPQ, APQ, and NNEa, reflecting an improvement of glottic closure and the voice quality. The F0 and SPL ranges, however, were reduced. The seventh patient presented with an improvement in glottic closure that was manifested in MPT and MFRc, but she developed incorrect phonatory behavior that was reflected in an increase in PPQ, APQ, and NNEa.

Computed Tomographic Findings. In all nine patients examined (63 to 2,156 days after injection) the injected silicone rubber was located in place (Fig 6). No evidence of migration was noted.

COMMENTS

As described earlier, the senior author has used different techniques including surgical augmentation, medial shift of the thyroid cartilage, and intrafold injections of three different methods over the past 30 years. Since we did not have modern techniques for objective voice evaluation in the early stage, we were not able to compare the functional results objectively among the surgical techniques. In perceptual evaluation, we did not find any differences in postoperative voice among the surgical techniques employed. The postoperative voice appears to have depended not on the surgical technique but chiefly on the surgeon's skill. Since 1983 we have employed transcutaneous intrafold injection in nearly all patients who needed surgical intervention for unilateral vocal fold paralysis. We have injected silicone rubber because Teflon has not been available in Japan. We have, therefore, had no opportunity to compare silicone and Teflon.

Transcutaneous intrafold injection was first reported by Seifert[4] in 1916. He inserted a needle into the subglottic lumen through the cricothyroid ligament and then penetrated the lower aspect of the vocal fold. The location of the needle was monitored under a laryngeal mirror. He injected paraffin successfully in two patients. In 1972, Hurst[5] reported another technique of percutaneous injection. He inserted a needle into the vocal fold through the cricothyroid space, without passing through the subglottic lumen, and injected Teflon. The location of the needle was monitored under a direct laryngo-

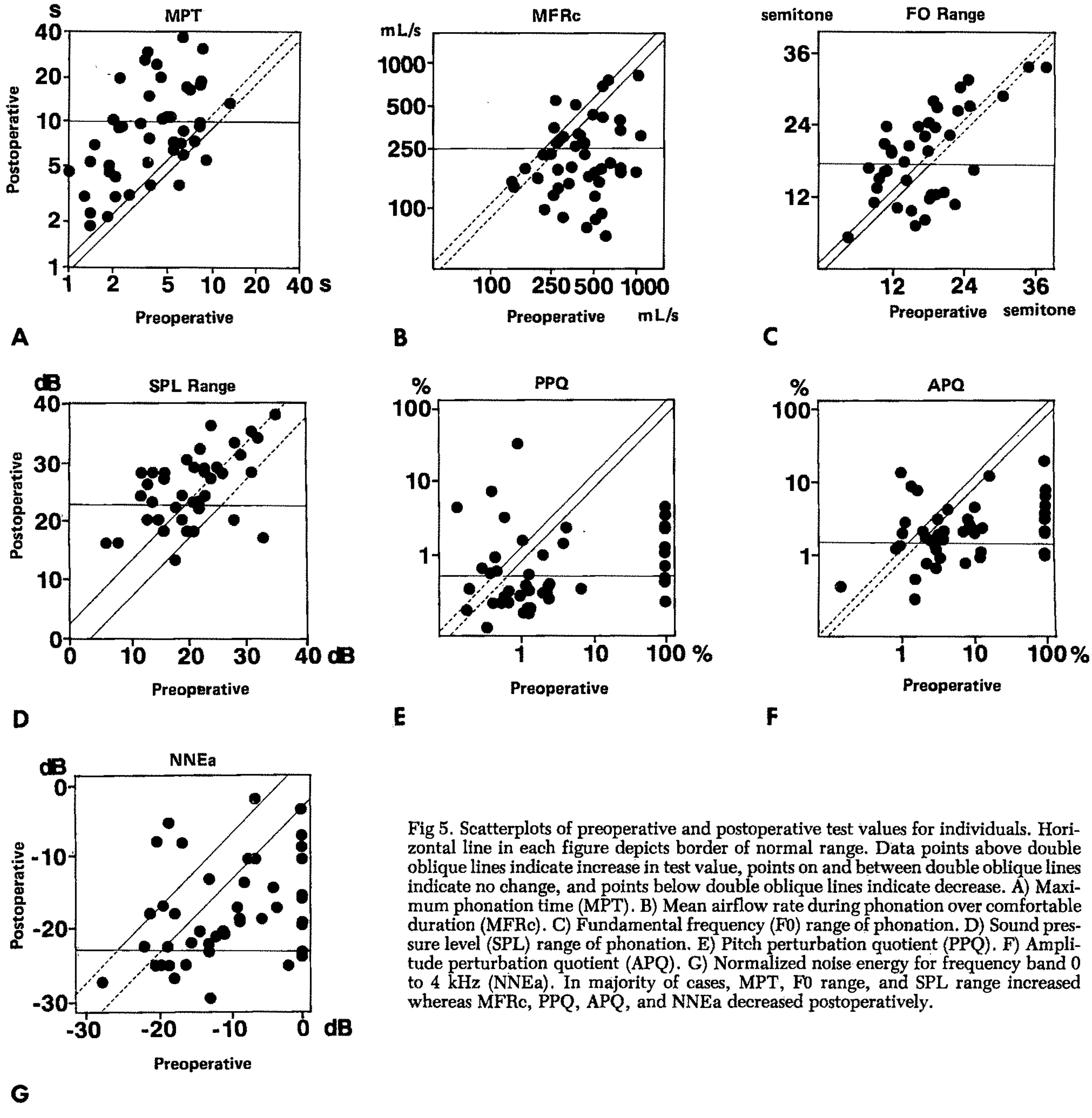

Fig 5. Scatterplots of preoperative and postoperative test values for individuals. Horizontal line in each figure depicts border of normal range. Data points above double oblique lines indicate increase in test value, points on and between double oblique lines indicate no change, and points below double oblique lines indicate decrease. A) Maximum phonation time (MPT). B) Mean airflow rate during phonation over comfortable duration (MFRc). C) Fundamental frequency (F0) range of phonation. D) Sound pressure level (SPL) range of phonation. E) Pitch perturbation quotient (PPQ). F) Amplitude perturbation quotient (APQ). G) Normalized noise energy for frequency band 0 to 4 kHz (NNEa). In majority of cases, MPT, F0 range, and SPL range increased whereas MFRc, PPQ, APQ, and NNEa decreased postoperatively.

scope. In 1985, two groups of laryngologists reported on transcutaneous injection: Ward et al[6] and Hirano et al.[2] The insertion technique that Ward et al employed was basically the same as that of Seifert. They monitored the location of the needle by means of a fiberscope or a telescope connected to a television screen. The report by Hirano et al was a preliminary report of the present study. Our route of needle insertion was basically the same as that of Hurst. We did not employ the route through the subglottic lumen because we were concerned about possible leakage of the injected material through the puncture hole at the lower surface of the vocal fold. Leakage occasionally takes place during transoral intrafold injection in which the upper surface of the vocal fold is punctured.

There have been many publications on surgical treatments for unilateral vocal fold paralysis. Reports of functional results based on objective evaluations, however, have been rather limited. Successful surgical treatments were manifested in an increase in MPT,[3,7-13] F0 range,[3,7-9,13] and SPL range[13]; a decrease in airflow rate during phonation[8,10,12-14] and phonation quotient[10,13,14]; improvements of sound spectrograms[3,8,15-18] including a reduction of noise, an increase in periodicity, and recovery of formant structure; and improvements of the vibratory pattern of the vocal fold viewed with ultrahigh-speed photography.[8] The vocal function is multidimensional. There is no single scale with which one can evaluate all its aspects. The choice of evaluation techniques should depend on the nature of the dis-

NUMBER OF PROCEDURES BY EVALUATION SCORE FOR EACH OF SEVEN TESTS

Score	*MPT*	*MFRc*	*F0 Range*	*SPL Range*	*PPQ*	*APQ*	*NNEa*
2	17	27	21	26	24	15	11
1	22	10	6	5	11	21	23
0	3	2	2	5	0	3	5
−1	2	5	10	3	9	5	5
Total	44	44	39*	39*	44	44	44
Total of scores 1 and 2	39 (89%)	37 (84%)	27 (69%)	31 (79%)	35 (80%)	36 (82%)	34 (77%)

MPT — maximum phonation time, MFRc — mean airflow rate during phonation over comfortable duration, F0 — fundamental frequency, SPL — sound pressure level, PPQ — pitch perturbation quotient, APQ — amplitude perturbation quotient, NNEa — normalized noise energy for frequency band 0 to 4 kHz.

*Data were not available for five procedures.

order. For unilateral vocal fold paralysis, we have currently been using three groups of tests, which have been described, ie, MPT and MFRc, which reflect the degree of glottic incompetence during phonation; F0 and SPL ranges, which roughly demonstrate the ability of F0 and SPL control; and PPQ, APQ, and NNEa, which show some important aspects of the voice quality. It takes approximately 20 to 25 minutes to complete the entire series of tests and obtain the test values.

There is no doubt that the degree of patient satisfaction is one of the important parameters of the success of surgical treatments for dysphonia caused by vocal fold paralysis. One cannot, however, depend simply on the patient's subjective evaluation in order to compare the results among different techniques, because the standard differs from patient to patient. A set of objective methods, therefore, should be employed. We think the test battery we have used in this study is one of the best existing methods that is realistic and clinically achievable.

The advantages of the transcutaneous silicone injection are as follows.

1. Unlike medialization operations, it does not call for any skin incision.
2. No general anesthesia is required. The procedure is conducted under topical anesthesia with minimum discomfort to the patient.
3. The patient does not need to open the mouth wide nor to have a rigid laryngoscope inserted in the throat.
4. The patient can phonate normally during the procedure. This allows the surgeon to evaluate the result with reliable visual and auditory monitors.
5. The working distance is short compared to that of injection under direct or indirect laryngoscopy.
6. The injected silicone does not migrate postoperatively.

The disadvantages are as follows.

1. The procedure cannot be applied to those patients who do not tolerate an injection into the throat in the awake state.
2. Two specialists are required: one to give the injection and the other to insert a fiberscope in the larynx.
3. The procedure calls for a fiberscope, a video camera, and a television.
4. The technique is slightly more difficult than the transoral intrafold injection. The surgeon needs to have had practice. For those laryngologists who are familiar with the needle insertion for electromyography of the thyroarytenoid muscle, the percutaneous injection is easy to conduct.

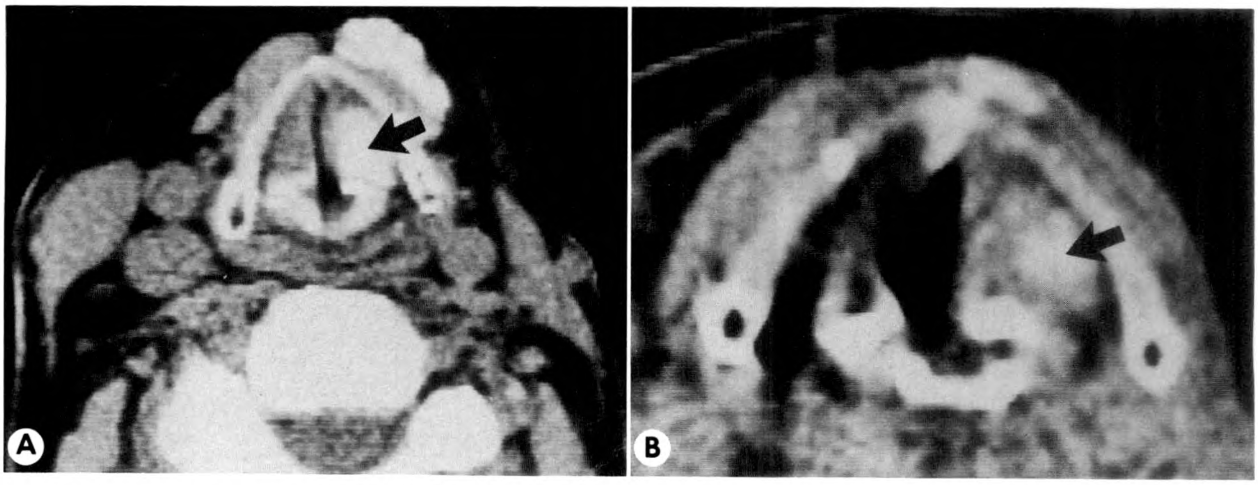

Fig 6. Computed tomograms demonstrating location of injected silicone (arrow). A) Seventy-eight-year-old woman, postoperative day 1,701. B) Seventy-six-year-old woman, postoperative day 1,062.

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ENDOSCOPIC LARYNGEAL SURGERY FOR BILATERAL MIDLINE VOCAL CORD OBSTRUCTION

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There are a number of treatment regimens for bilateral laryngeal paralysis, ranging from tracheostomy to external microscopic approaches. None has become the standard because of their unpredictable results and/or the need for an external approach. Recently, the use of micro-trapdoor flaps and suturing done via a laryngoscope has shown a possibility of correcting the airway problem, allowing a predictable result, with a completely endoscopic approach. This paper presents our experience with a group of 10 patients who had at least one treatment attempt that failed and were treated by endoscopic laryngoplasty. Eight have been decannulated.

KEY WORDS — endoscopy, laryngeal obstruction, laryngeal surgery, vocal cord fixation, vocal cord paralysis.

INTRODUCTION

Laryngeal obstruction due to bilateral abductor vocal cord paralysis and bilateral vocal cord fixation has been the subject of many treatment regimens. The ideal procedure would endoscopically move the vocal cords off the midline, restoring the airway while leaving a normal voice. In real life there is a trade-off between a good airway and a good voice.

There are many treatment regimens for bilateral midline vocal cord obstruction. Tracheostomy to produce an airway has always been an option that is simple and relatively safe. However, this procedure does not restore the larynx to independent function. A variety of external approaches have been described and advocated.[1-6] These all have been successful to various degrees in achieving decannulation, but require an external approach for the thyrotomy and/or arytenoidectomy. If decannulation is achieved, the voice may be breathy and there may be residual scarring.

Endoscopic procedures include that of Thornell,[7] which removes the arytenoid by electrocautery, and that of Ossoff,[8] which removes the arytenoid by laser ablation. While these procedures have produced an airway, there is a breathy voice and a significant chance of posterior glottic scarring that negates the effect of arytenoid cartilage removal. To correct this problem Dedo and Sooy[9] and later Duncavage et al[10] have used small inferiorly based mucosal flaps to cover the exposed submucosa, and they have been successful.

We report our experience with an endoscopic laryngoplasty that incorporates inferiorly based micro-trapdoor mucosal flaps, a carbon dioxide (CO_2) laser, and an endoscopic suturing technique to treat bilateral vocal cord paralysis.

MATERIALS AND METHODS

WORKUP

There are two important considerations to understanding the laryngeal state of these patients. First, because these patients have had laryngeal trauma or have already been treated, a review of the prior history cannot be overemphasized. The mechanism of obstruction, whether neurogenic, traumatic, or inflammatory, will indicate the type of vocal cord paralysis. The method and extent of any arytenoidectomy, along with what means were used to tie or scar back the posterior lateral glottis, will determine the underlying disorder to be found. Specifically, the Woodman procedure ties back the vocal process and may injure the posterior commissure. Some surgeons have recommended that the bed of the arytenoidectomy after an endoscopic laser procedure should undergo electrocoagulation, which leads to scar shelves in the posterior commissure and the lateral corner of the posterior glottis. Dilations with steroid injection may predict a scarred corner of the posterior glottis, although the submucosa may not be as densely fibrotic.

Second and equally important, failure to completely clear the hypopharynx by swallowing is a sure predictor of failure. All of these operations may leave an anatomic defect in the glottis and a ready route for aspiration. Evaluation by barium swallow x-ray study must be done to confirm good clearance through the upper esophageal sphincter. Any obstruction should be investigated as to the presence of a mass, fixed closure (eg, scarring of the cricopharyngeus after irradiation), or failure of the larynx to rise and open the upper esophageal sphincter. Inability to correct upper esophageal obstruction is an absolute contraindication to a posterior glottic procedure.

P 35482

TECHNIQUE

Anesthesia. The anesthetic is always adminis-

Presented at the meeting of the American Laryngological Association, Palm Beach, Florida, April 28-29, 1990.

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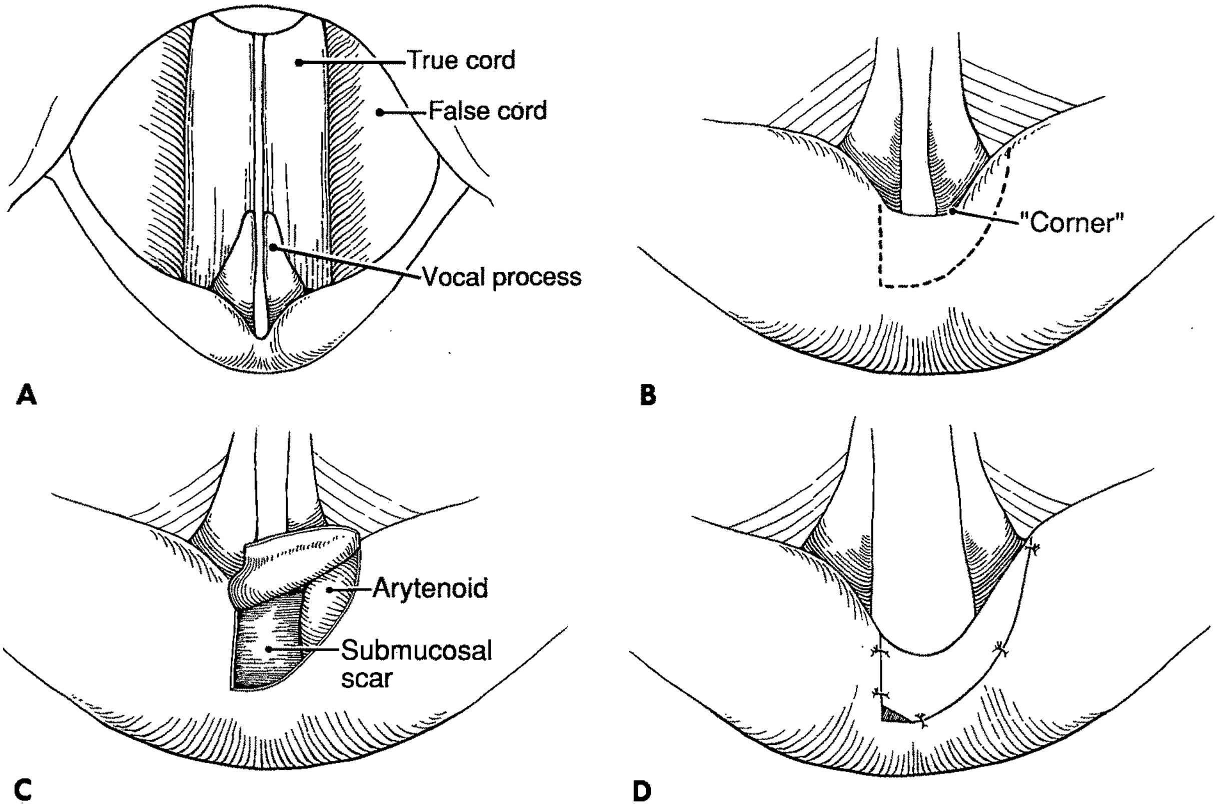

Fig 1. Basic laryngoplastic procedure. A) Bilateral midline vocal cord paralysis. B) Incision to free posterior wall scarring that opens inferiorly based mucosal flap from "corner" of scarred posterior glottis. C) Removal of submucosal scar tissue in plane between mucosa and interarytenoid muscle with carbon dioxide laser. D) Mucosal flap closed with polyglycolic suture. Note there may be bare area left because of release of arytenoid from scar or because of flap foreshortening. This bare area should be left over flat posterior wall of glottis and not at "corner."

tered via a tracheostomy. A metal tracheostomy tube is used to prevent the errant laser ignition that might occur with a plastic tube. Usually an endotracheal tube is cut and wedged into the metal tracheostomy. There is not a tight seal of the trachea and anesthetic gases can escape upward as the glottis is opened. A suction catheter placed near the glottis is used to scavenge gases away. Soaked cotton sponges can be packed below the cords to help seal the trachea as long as they can be all accounted for. With these precautions there is no need to cut oxygen levels. The advantages of this arrangement are the ease of visualizing the posterior glottis, the control of breathing, and even the ability to perform these procedures on an outpatient basis.

Equipment. Any scope may be used, but none smaller in diameter than the adult Dedo laryngoscope. The posterior half of the glottis must be in the lower field of view. To the Dedo laryngoscope with the large No. 2 fiberoptic cables an extra tube has been soldered to scavenge smoke and steam as well as anesthetic gases. This tube reduces the need for hand-held suctioning. The illumination with this scope is excellent and avoids the need for proximal lighting from the microscope, which causes a tiring and distracting reflection from the proximal laryngoscope.

The lasers used are CO_2. The power settings are set as low as possible to cause little tissue injury yet achieve a speed and efficiency of resection. Thus, the mucosa is opened with 5 W of power and 0.05-second pulses. A repeat mode is often used. Where lateral dispersion of energy is not a worry, up to 20 W on continuous or repeat mode can be used with 0.10- or 0.20-second bursts. Then, as the final end of resection is approached, the energy levels are set back down. Both a 0.8- to 1.0-mm spot size and microspot apparatus have been used, depending on the operating room.

Basic Procedure. All of the operations are a variation of a basic procedure, that of submucosal scar removal through a micro-trapdoor flap. The basic operation is described in Fig 1. The theory behind this approach is to enter the submucosa through a tiny mucosal flap, remove scar or cartilage, and leave only a well-sutured incision and no open areas that can scar around the "corner." It is the raw and uncovered "corner" that heaps up granulation tissue and eventually heals leaving a scarred shelf that fills in the defect so carefully created by the procedure (H. Dedo, personal communication, 1987) (Fig 2). It is important to plan incisions so they are placed away from this "corner" and so that the flap created is not perforated or poached by the laser dissection. The mucosal edge will be less damaged when the laser is set to as low a power as possible,

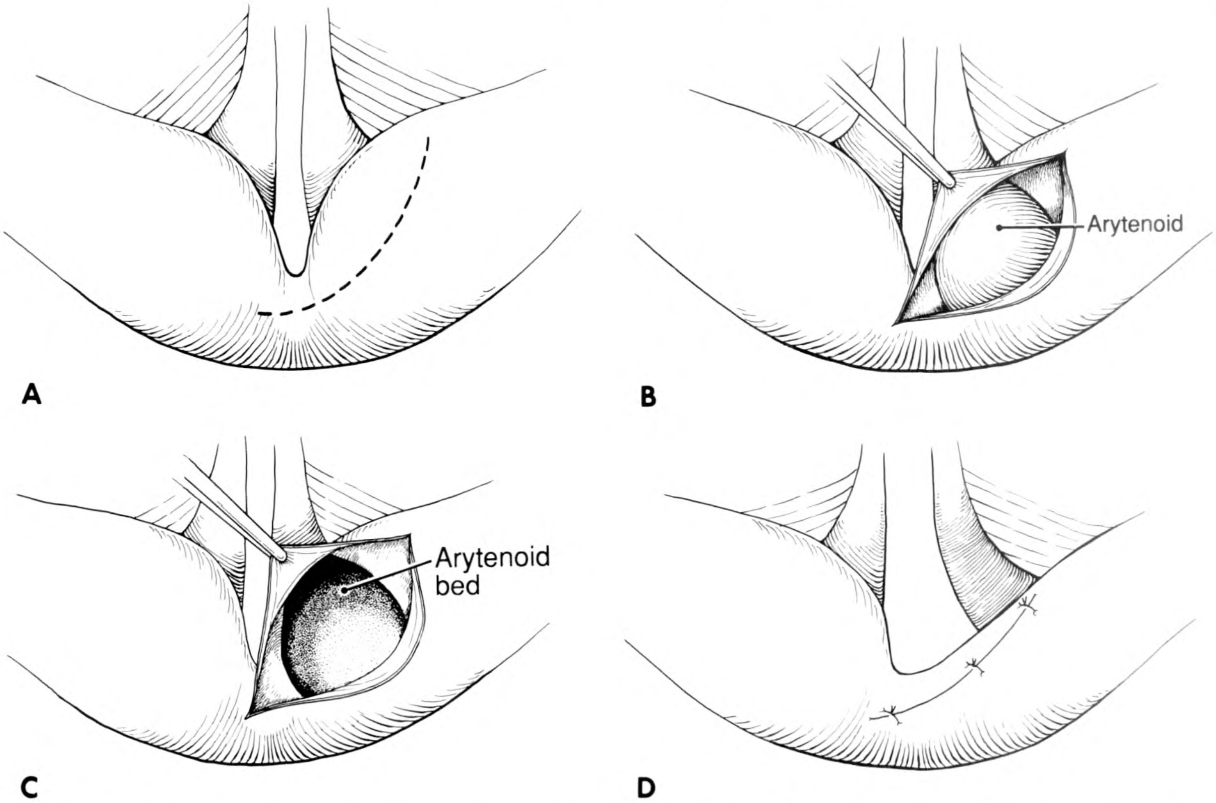

Fig 2. Arytenoidectomy variation of basic laryngoplasty. A) Incision is moved laterally, but extends to midline to assure good coverage of posterior laryngeal "corner." B) Inferiorly based mucosal flap exposes corniculate cartilage, body of arytenoid, and vocal process. C) Arytenoid has been removed. Note that least amount of trauma to bed produces best result. In some patients body of arytenoid may be resected to leave outer shell of cartilage. Posterior and lateral cricoarytenoid muscles and interarytenoid muscles are still attached and will function to move arytenoid if cricoarytenoid joint is not disturbed. D) Incision is closed precisely with polyglycolic sutures to leave no bare area. Posterior glottis, so important for respiration, is opened, and membranous vocal cord will allow voice to form.

intermittent pulses are used, and the tissue has time to cool between exposures. If relaxation incisions are needed that leave a bare segment, they should be placed out of the "corner." For ease of tying, the suture material is the synthetic (polyglycolic acid) material rather than chromic. Local steroid injections are avoided because they tend to slow down re-epithelialization. No stents are used.

Variations of Basic Procedure. For patients who have bilateral fixed cricoarytenoid joints and may have undergone previous dilation and steroid injection, arytenoidectomy is the next logical treatment approach (Fig 2). The procedure after raising a flap is not too different from that described by Ossoff,[8] except the posterior membranous vocal cord is not resected. Care in not injuring the cricoid cartilage prevents removal of too much of the posterior commissure, excessive granulation tissue, and possible aspiration problems. Relaxation incisions are usually not necessary, although a suture to obliterate the "dead" space may be necessary. In two patients the arytenoid was removed to leave only the outer shell with the lateral and posterior cricoarytenoid and interarytenoid muscles attached. The cricoarytenoid joint was not entered. This method allows a better airway, while not hindering the return of arytenoid motion.

For patients with scarring posteriorly but a mobile cricoarytenoid joint, removal of the submucosal scar tissue and/or a partial arytenoidectomy will free the arytenoid to work again. A shelf of scar is appreciated over the posterior commissure by using the laryngoscope to gently separate the two arytenoids. The basic incision is extended laterally over the one arytenoid prominence. The underlying scar tissue is removed. The scar usually involves the submucosa between the mucosa and the underlying interarytenoid muscles. The muscle does not need to be cut. The flap is laid back into the defect. If the interarytenoid distance has increased as the arytenoid is released, the flap is split. This split should be placed to leave any bare submucosa, not in the "corner," but rather in the flat area of the posterior glottic wall (Fig 1D).

If the arytenoid is bound into this scar, a portion of the arytenoid can be removed. The laser resection of the scarring is extended into the body of the arytenoid, but leaves a shell of the cartilage laterally. Care is taken not to injure the cricoarytenoid joint, in order to leave the muscular and vocal processes intact so that the arytenoid can still cause adduction and abduction of the cord.

In failures of the Woodman procedure, a shelf of

BREAKDOWN OF PATIENT EXPERIENCE

Pt	*Age (yr)*	*Sex*	*Medical Status*	*Diagnosis*	*Previous Operations*
1	34	F	Normal	Intubation scarring	Granuloma removal and cortisone injection
2		F	Normal	Intubation scarring	None
3	65	F	Normal	Intubation scarring	Dilation and cortisone injection
4	63	M	Status post CABG	Intubation scarring and arytenoid fixation	Arytenoidectomy, dilation, and cortisone injection
5	61	M	Pulmonary fibrosis	Irradiation perichondritis	Irradiation
6	62	F	Cardiac	Intubation scarring	Dilation and cortisone injection
7	65	F	Normal	Polio paralysis	Tracheostomy
8	62	F	Status post CABG	Intubation scarring and arytenoid fixation	Left arytenoidectomy
9	62	F	Normal	Thyroidectomy	External arytenoidectomy x2
10	62	M	Right heart failure	Teflon injection reaction	Excision of Teflon

CABG — coronary artery bypass graft.

dense scar is found in the "corner." The basic operation is used to remove scar tissue. With removal of the scar there is no need to remove the remaining vocal process. Suture material has been seen and should be taken out or at least vaporized from the bed. Again the split in the flap should be made just medial to the "corner."

Postoperative Care. Postoperatively, the patients are given antibiotics and steroids, orally, for a week. They may eat and resume normal activities. In fact, except for those patients with a new tracheostomy, the procedure is done on an outpatient basis. There is little pain. Patients are followed on a weekly basis. If there is a resumption of swelling in the glottis, a second course of antibiotics and steroids is given. The usual healing time before decannulation is approximately 2.2 months. The swelling disappears as the sutures are absorbed.

RESULTS

Ten patients have been operated on with these techniques. The Table shows the distribution of cases. All of these patients have at least a 1-year follow-up.

In this series successful decannulation has been achieved in 8 of the 10 patients (80%). The activity level to which the successful patients returned is "full" in all but those who felt that their underlying cardiac condition prevented normal activity. In reality they were not hampered by the laryngeal airway, but by their underlying cardiopulmonary status. The voices, as rated by the patients, varied between a normal voice in cases in which the posterior wall scarring had been released and the somewhat coarse breathiness of the arytenoidectomy patients. All felt that their voices were very usable. Of the 80% successful patients, none complained of any aspiration.

Of interest are the excellent results in patients who had had previous arytenoidectomy either as an external procedure or as an endoscopic procedure. Removing the underlying scar tissue and carefully covering the defect prevented re-formation of the obstruction.

Note the two patients who were treated by removal of a portion of the arytenoid that left the muscles attached. Both patients had fixation of the opposite cord from other procedures. The healed arytenoid moves, abducts to give a good airway, and produces a voice that is excellent in one patient and good in the other.

The two patients who failed endoscopic laryngoplasty did so because of aspiration. In one, an attempt was made to remove an arytenoid to open an airway edematous from postirradiation perichondritis. The cartilage was found to be replaced by a very thick perichondrium that made closure of the operative defect very difficult. Added to this was edema and stiffness of the cricopharyngeus muscle that could not be appreciated because the preoperative larynx was closed by edema. The arytenoid defect and the obstruction to flow led to aspiration and an eventual laryngectomy. The other patient had had polio that left her with vocal cord paralysis, cricopharyngeus spasm, and paralysis of the palate. While she was treated for her laryngeal and cricopharyngeal problems, she would not allow treatment of the soft palate. Because of fears of aspiration, this patient will not try to swallow without a tracheostomy in place.

DISCUSSION

Thyroidectomy, tuberculosis, and diphtheria used to be the most common causes of bilateral midline vocal cord paralysis. Whited[11] has well described the emergence of the endotracheal tube as

BREAKDOWN OF PATIENT EXPERIENCE (Continued)

Operation Used	*Time to Decannulation (mo)*	*Activity Level**	*Evidence of Aspiration*	*Quality of Voice**	*Follow-up*
Basic laryngoplasty	2	Full	None	Normal	6 yr
Basic laryngoplasty	1	Full	None	Normal	5 yr
Laryngoplasty and arytenoidectomy	3	Full	None	Slightly breathy	4 yr
Laryngoplasty and excision of scar in arytenoid bed	1.5	80%	None	Moderately breathy	2 yr
Laryngoplasty and arytenoidectomy	Never	Worse	Constant	Breathy	Laryngectomy performed
Basic laryngoplasty	44†	80%	None	Excellent	2 mo
Laryngoplasty and arytenoidectomy	Never	Full but afraid to be decannulated	None	Moderately breathy	1.5 yr
Laryngoplasty and partial right arytenoidectomy	1	Full	None	Excellent	2 yr
Basic laryngoplasty	2	Full	None	Slightly breathy	2 yr
Laryngoplasty and partial arytenoidectomy	5	80%	None	Slightly breathy	1 yr

*As rated by patients.

†Tracheostomy remained because of operation for brain tumor.

the primary cause of midline vocal cord paralysis today. Prolonged use, too large a tube, and too much patient movement relative to a tube fixed by the ventilator lead to early mucosal erosion and eventual chondritis, arthritis, and even recurrent nerve inflammation.

Hirano et al[12] have used whole sections of the larynx to describe the anatomy of the posterior larynx. Of importance to this work is the layer of both loose and fibrous submucosal tissue in the posterior laryngeal wall that is separate from the interarytenoid muscle and yet liable to become fixed from inflammation. Scar tissue here does not enter the interarytenoid muscle, and removal of the scar allows this muscle to contract and relax in a normal fashion. Hirano et al also measured the posterior larynx and determined that this is the most important area for maintaining the airway. Thus, major improvements in laryngeal airflow can be accomplished by moving the arytenoid from the midline or by resecting all or a part of the arytenoid.

Fink[13] and Fink and Demarest[14] have shown that the recoil action of the elastic cartilages of the larynx and the tracheobronchial tree is set to separate the vocal cords and open the airway. Thus, a release of scar tissue holding the arytenoids together will allow these cartilages to move away from the midline automatically. Stenting the larynx open is not necessary if the arytenoids are completely freed from cicatrix. In fact, experiments in laboratory animals seem to indicate that stenting may lead to scar formation.[15]

The authors believe that the success of this procedure is related to six factors. First, the use of micro-trapdoor flaps allows coverage of the exposed submucosa. Second, the lateral "corner" between the posterior glottic wall and the posterior vocal cord (including the arytenoid) must be covered to prevent a shelf of scar from forming and negating the results of the resection. Any open submucosa that must be left exposed should be placed over the flat area of the posterior glottic wall. Third, the CO_2 laser must be set so as not to injure the mucosal flap. Fourth, the scar tissue must be removed to release the arytenoid and facilitate its natural tendency to abduct. Fifth, stents are to be avoided, as they may repeat the initial scarring as would an endotracheal tube. Sixth, suturing is very important to guarantee that the micro-trapdoor flap will remain in place and effect permanent coverage.

Any procedure on the injured larynx must take into account the problem of aspiration. Obstruction to swallowing and the production of a defect in the glottis is an invitation for foreign material to enter the tracheobronchial tree. Insightful workup of the patient while one is contemplating laryngoplasty is the only way to avoid this problem.

CONCLUSION

The method presented here has the advantages of an endoscopic approach and the avoidance of any endolaryngeal stenting devices. It has been successful in the treatment of patients who have failed other forms of external and endoscopic opening of the larynx. While the ultimate technique would restore vocal cord function completely, we feel confident that this procedure offers a relatively secure means of laryngeal rehabilitation.

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MEDICAL COMPLICATIONS IN TOTAL LARYNGECTOMY: INCIDENCE AND RISK FACTORS

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The prevention and management of medical complications are important components in the surgical treatment of head and neck malignancies. We retrospectively evaluated the postoperative medical complications in 414 patients who underwent total laryngectomy between 1973 and 1987. The mortality rate was 1.2% (five deaths); while major, nonfatal medical complications occurred in 6.3% (24 of 384 patients) — seven strokes, three myocardial infarctions, two pulmonary emboli, and 12 respiratory failures requiring mechanical ventilation. Elderly patients did not experience more frequent or more severe medical complications, and the overall pattern of complications was different from that of other surgical specialties. Only specific cardiovascular and pulmonary risk factors were associated with these complications. We conclude that medical complications are a significant cause of morbidity in total laryngectomy; a focused preanesthetic risk factor analysis by a medical team familiar with head and neck cancer patients assures prompt identification and management of these complications.

KEY WORDS — medical complications, total laryngectomy.

INTRODUCTION

The medical complications of surgical procedures are especially important considerations in head and neck surgery because of the high incidence of comorbidity in patients with upper aerodigestive tract tumors. In addition, the socioeconomic pressures of an aging population and cost containment measures implemented by reimbursement agencies make a better understanding of risk factors for surgical morbidity crucial to developing strategies to minimize postoperative complications.

This study examines the preanesthetic risk factors and correlates these factors with the incidence and significance of postoperative complications in patients undergoing total laryngectomy.

METHODS

The medical records of patients undergoing total laryngectomy by the University Otolaryngology Group at the Eye and Ear Hospital of the University of Pittsburgh School of Medicine between 1973 and 1987 were reviewed. This included patients undergoing neck dissection or extended pharyngectomy with total laryngectomy. Data were collected on patient age, sex, tumor stage, operations performed, American Society of Anesthesiologists (ASA) physical status category, medical risk factors identified by history and physical examination, operative duration, postoperative surgical complications, medical complications, and duration of hospitalization.

Preoperative Conditions. Criteria for recording preoperative comorbidity were as follows. Hypertension, angina, chronic obstructive pulmonary disease (COPD), liver disease, kidney disease, and diabetes mellitus were recorded as present if the patient was receiving medical therapy for the condition at the time of operation. Severe COPD, congestive heart failure, or stroke was recorded as present if the patient had ever required hospitalization for the condition. Previous myocardial infarction was recorded according to the cardiologist's interpretation of the electrocardiogram (ECG), and significant cardiac murmurs were recorded if a medical consultant had recommended antibiotic prophylaxis for the condition.

Postoperative Complications. Criteria for the four major medical complications were as follows.

1. Respiratory failure: mechanical ventilation required for more than 24 hours postoperatively or initiated during the postoperative period.
2. Stroke: a new medically documented neurologic deficit of central origin.
3. Myocardial infarction: new ECG changes or elevated creatinine phosphokinase myocardial fraction consistent with myocardial infarction.
4. Pulmonary embolus: diagnostic defects on pulmonary angiography or high probability as indicated by ventilation-perfusion scanning.

Medical diagnoses were confirmed by medical specialists, and their clinical diagnoses alone were the criteria for recording minor medical complications in this study.

Statistical Evaluation. Statistical evaluation was performed with χ^2 analysis for discrete variables and Student's *t* test for continuous variables.

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Presented at the meeting of the American Laryngological Association, Palm Beach, Florida, April 28-29, 1990.

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TABLE 1. AGE DISTRIBUTION OF 414 PATIENTS WITH TOTAL LARYNGECTOMIES ACCORDING TO TUMOR STAGE AND ADDITIONAL PROCEDURES PERFORMED

	*≥65 yr (n = 184)**		*<65 yr (n = 230)†*	
	No.	*%*	*No.*	*%*
Tumor stage				
I	2	1	1	0.4
II	19	10	30	13
III	122	66	116	50
IV	40	22	83	36
Procedures				
TL	63	34	59	26
+ ND	101	55	122	53
+ BND	12	7	23	10
> TL	8	4	26	11

TL — total laryngectomy alone, + ND — total laryngectomy and unilateral neck dissection, + BND — total laryngectomy and bilateral neck dissection, > TL — extended laryngectomy with myocutaneous or free flap reconstruction and unilateral or bilateral neck dissection.

*Nine patients were >80 years; 175 were 65 to 80 years. Staging information was unavailable for 1 patient.

†Forty-two patients were <50 years; 188 were 50 to 64 years.

RESULTS

During this interval, 414 patients underwent total laryngectomy; complete chart information was available for 384 patients. Accordingly, the frequency of procedures and complications was recorded on the 414 patients (Tables 1 and 2); however, risk factor analysis was performed on the 384 with complete information. The ages ranged from 28 to 90 years; the mean age was 62 ± 9 years, and 184 patients were 65 years or older (Table 1). The tumor stages and additional operative procedures were similarly distributed among the elderly and younger patients.

Table 2 summarizes the incidence of major postoperative complications and duration of hospitalization according to the operative procedures performed. Pharyngocutaneous fistulas were more frequent in patients undergoing extended laryngectomies with flap reconstructions ($p < .05$), and postoperative strokes occurred only in patients who underwent neck dissections. Specific operative procedures were not otherwise associated with higher complication rates ($p > .05$).

The overall 30-day postoperative mortality rate was 1.2% (five deaths), with no operative or perioperative deaths. One patient died of a ruptured abdominal aortic aneurysm, while the other four died of cardiac complications with cardiopulmonary arrest as the final event.

Table 3 summarizes the medical complications in this series. Serious, nonfatal medical complications occurred in 24 of the 384 patients (6.3%), including seven strokes, three myocardial infarctions, and 12 postoperative respiratory failures requiring mechanical ventilation. Of particular note is that only two (0.5%) pulmonary emboli were observed.

Minor complications resolved promptly with therapy and did not have a long-term health impact on the patient. Pulmonary complications were the most frequent postoperative medical complications in this series. Exacerbations of COPD, pneumonitis, and pulmonary edema occurred in 83 patients (21.6%). Gastrointestinal complications were uncommon and included seven cases of prolonged ileus and four minor episodes of bleeding gastritis. Total parenteral nutritional support was complicated by septic, metabolic, or central venous catheter complications in 13 patients.

The surgical complications of these 384 total laryngectomies are summarized in Table 4. Major complications occurred in 57 patients (15%). The rate of pharyngocutaneous fistulas was 10% in total laryngectomies performed as the sole procedure or with unilateral or bilateral neck dissection (35/350). One patient with a pharyngocutaneous fistula also suffered a carotid erosion that resulted in hemispheric stroke following an emergency carotid ligation.

The mean length of hospitalization in this series was 14.5 ± 11 days. Table 5 lists the complications according to the length of hospitalization. Except for pulmonary embolism, major surgical and medical complications were associated with prolonged hospitalization ($p < .05$). In addition, postoperative pneumonia, pulmonary edema, ECG changes, and postoperative hemorrhage resulted in lengthened hospitalization ($p < .05$).

According to the corresponding organ system, significant risk factors were associated with medical complications. Table 6 summarizes the preanesthetic risk factors identified in this series. The predomi-

TABLE 2. INCIDENCE OF MAJOR COMPLICATIONS, OPERATING ROOM TIME, PHYSICAL STATUS CATEGORIES, AND LENGTH OF HOSPITALIZATION ACCORDING TO OPERATIVE PROCEDURES IN 414 TOTAL LARYNGECTOMIES

				Death		*Fistula*						
Procedure	*No.*	*OR Time (hr)*	*PS*	*No.*	*%*	*No.*	*%*	*CVA*	*PE*	*MI*	*Vent*	*Days*
TL	122	3.5	2.6	1	0.8	6	4.9	0	0	1	1	12.3
+ ND	224	4.6	2.6	3	1.3	29	12.9	4	2	0	9	15.0
+ BND	34	5.8	2.7	1	2.9	6	17.6	1	0	1	2	16.9
> TL	34	5.7	2.5	0		13	38.2	2	0	0	0	17.7

OR — operating room, PS — American Society of Anesthesiologists physical status category, Death — mortality from start of operation to 30 days (all occurred as "postoperative," >48 hours postop and <30 days postop), Fistula — pharyngocutaneous fistula documented radiographically or diagnosed clinically during hospitalization, CVA — new stroke diagnosed postoperatively, PE — pulmonary embolus, MI — myocardial infarction, Vent — respiratory failure, Days — days hospitalized postoperatively, TL — total laryngectomy alone, + ND — total laryngectomy and unilateral neck dissection, + BND — total laryngectomy and bilateral neck dissection, > TL — extended laryngectomy with myocutaneous or free flap reconstruction and unilateral or bilateral neck dissection.

TABLE 3. POSTOPERATIVE MEDICAL COMPLICATIONS IN 384 TOTAL LARYNGECTOMIES

Complications	*No.*	*%*
Major		
Mechanical ventilation	12	3.1
Stroke	7	1.8
Myocardial infarction	3	0.8
Pulmonary embolus	2	0.5
Minor		
Chronic obstructive pulmonary disease exacerbation	33	8.6
Pneumonia	29	7.6
Pulmonary edema	21	5.5
Cardiac arrhythmia requiring therapy	17	4.4
Confusion	16	4.2
Complications with parenteral hyperalimentation	13	3.4
Urinary tract infections	13	3.4
Angina	11	2.9
Urinary obstruction	9	
Hypertension	8	
Functional ileus (>5 d)	7	
Drug withdrawal	5	
Gastrointestinal bleeding	4	
Maxillary sinusitis	3	
Hypocalcemia	3	
Decubitus ulcers	1	
Transfer to nursing home (temporary)	1	
Grand mal seizure	1	
Suicidal ideation	1	
Loss of pacemaker function (temporary)	1	
Venous thrombophlebitis	1	
Antibiotic allergy	1	

TABLE 4. SURGICAL COMPLICATIONS IN 384 TOTAL LARYNGECTOMIES

Complications	*No.*	*%*
Major		
Pharyngocutaneous fistula*	48	12.5
Postoperative hemorrhage	7	1.8
Carotid erosion	1	0.3
Chyle fistula	1	0.3
Minor		
Wound infection	52	13.5
Facial edema	10	2.6
Tracheoesophageal puncture and neoglottis aspiration	5	1.3
Intraoperative aspiration	2	
Hematoma	2	
Corneal abrasion	2	
Intraoperative hypotension	1	
Seroma	1	
Hypoglossal paralysis	1	
Phrenic paralysis	1	

*Incidence in total laryngectomy alone or with unilateral or bilateral neck dissection was 35 of 350 (10%).

nant preanesthetic risk factors reflect significant alcohol and tobacco abuse, known predisposing factors to upper aerodigestive tract carcinoma. In Table 7, corresponding risk factors are listed according to the complications that occurred more frequently ($p < .05$) in those patients. Postoperative mortality was associated with a history of stroke or the presence of a significant cardiac murmur; strokes were associated with a history of diabetes mellitus; respiratory failure requiring mechanical ventilation was associated with a history of severe COPD or wheezing on preoperative physical examination. When surgical complications were studied as risk factors, pharyngocutaneous fistulas were associated with postoperative pneumonia ($p < .05$). This relationship is not surprising in light of the proximity of the fistulous tracts to the tracheostomas. Preanesthetic physical status categories, tumor stage, and operative time did not predict medical complications ($p > .05$).

Table 8 illustrates that the elderly experienced medical complications more frequently than patients younger than 65 years ($p < .05$); however, *major* medical complications (ie, respiratory failure, myocardial infarction, pulmonary embolus, and stroke) were not significantly more frequent in the elderly ($p > .05$.) Furthermore, although the elderly had more frequent risk factors for complications than younger patients, this trend was not significant ($p > .05$); and the occurrence of complications did not result in longer hospitalizations for the elderly than for younger patients with the same complications (Table 5). The mean length of hospitalization was 14 days for the elderly and 14.9 days for patients less than 65 (Table 8).

The extremely poor medical condition of two patients was improved by total laryngectomy. Both patients were 90 years of age, with aspiration pneumonitis, significant cardiac arrhythmias, and mental obtundation; after total laryngectomy, the absence of aspiration resolved the pneumonitis and hypoxia-related arrhythmias.

DISCUSSION

The head and neck cancer patients in this series exhibited very similar rates of preanesthetic risk factors as the elderly patients who underwent operations in different surgical specialties in Stephen's[1] series of 1,000 consecutive patients over age 70. The major distinction is the higher incidence of COPD in our series, 68% versus 14%. Yet, despite the similarity of preanesthetic risks, the postoperative mortality in the general surgery patients[1] was predominantly due to sepsis, acute renal failure, carcinomatosis, and acute respiratory failure. These causes of death were not encountered in the 1.2% mortality of our series of total laryngectomies. The more frequent occurrence of cardiac death and severe pulmonary complications in the laryngectomy patients may be attributed to the almost universal tobacco abuse among these patients as reflected in the incidence of COPD in head and neck cancer patients.

However, since the differences in preanesthetic risks only partially explain the different postoperative complications of these head and neck cancer patients, the systemic stresses of total laryngectomy versus non-head and neck operations must be con-

TABLE 5. LENGTH OF POSTOPERATIVE HOSPITALIZATION ACCORDING TO POSTOPERATIVE COMPLICATIONS AND AGE IN 384 TOTAL LARYNGECTOMIES

Complications	*Mean Length of Hospitalization (d)* ≥ 65 *yr*	< 65 *yr*	*Overall*
Medical			
Mechanical ventilation	25	23	25*
Stroke	29	77	43*
Myocardial infarction	11	88	36*
Pulmonary embolus	15	9	12
Chronic obstructive pulmonary disease exacerbation	14	24	19
Pneumonia	27	25	23*
Pulmonary edema	19	54	24*
Cardiac arrhythmia requiring therapy	22	37	30*
Confusion	14	25	18
Angina	21	15	18
Urinary obstruction	14	11	14
Surgical			
Pharyngocutaneous fistula	31	33	32*
Postoperative hemorrhage	—	34	34*
Carotid erosion	—	130	130*
Chyle fistula	28	—	28*
Wound infection	19	17	18

Overall mean hospitalization was 14.5±11 days.

*Prolonged postoperative hospitalization ($p < .05$).

TABLE 6. PREANESTHETIC MEDICAL RISK FACTORS IN 384 TOTAL LARYNGECTOMIES

Risk Factors	*No.*	*%*
History		
Chronic obstructive pulmonary disease	264	68.8
Hypertension	133	34.6
Active alcohol abuse	94	24.5
Angina	61	15.9
Myocardial infarction	53	13.8
Diabetes mellitus	43	11.2
Severe chronic obstructive pulmonary disease	37	9.6
Congestive heart failure	32	8.3
Stroke	23	5.9
Liver disease	14	3.6
Kidney disease	5	1.3
Physical examination		
Significant heart murmur*	32	8.3
Pulmonary wheezing	10	2.6
Carotid bruit	7	1.8
Third heart sound	3	0.8
Distension of jugular vein	1	0.3
Tests		
Abnormal electrocardiogram	133	34.6
Abnormal chest radiograph	56	14.6

*Confirmed by medical consultant and considered significant enough to warrant antibiotic prophylaxis.

sidered a major explanation for the different morbidity. Except for deglutition and phonation, head and neck procedures leave basic physiologic functions undisturbed. These patients resume ambulation promptly and only rarely experience altered gastrointestinal and genitourinary function.[2] Head and neck surgery poses different physiologic stresses than other surgery. In fact, the aerodigestive separation accomplished by total laryngectomy can resolve life-threatening aspiration.

Thromboembolic disease occurring as deep venous thrombosis or pulmonary embolism is a significant cause of postoperative morbidity in general and orthopedic surgery.[3] However, this has not been a significant cause of morbidity in head and neck surgery. The incidence of pulmonary embolism was 0.52% in our series of total laryngectomies and 0.26% in a British series of 374 total laryngectomies.[4] Studies employing radiolabelled fibrinogen indicate that even clinically undetected deep venous thrombosis is less frequent in head and neck surgery than in other surgical procedures (C. Snyderman, personal communication, 1989). The explanation of this phenomenon is unclear, and the previous opinion that early ambulation minimizes thromboembolic disease in head and neck surgery is incompatible with evidence that the deep venous thrombi form intraoperatively.[3]

In this era of prospective reimbursement, the fact that postoperative medical complications increase the length of hospitalization signifies financial losses in addition to the morbidity of those complications. Head and neck surgeons thus face an added urgency to minimize the complications of these procedures.

The surgical morbidity of laryngectomy, along with strategies to avoid and manage those complications, has been reviewed in detail elsewhere.[5,6] However, this series illustrates that the medical complications are also significant sources of morbidity in head and neck surgery that may be predictable from the preanesthetic evaluation.

The ASA physical status is generally a reliable predictor of serious postoperative medical morbidity.[7] However, the prevalence of serious systemic diseases among head and neck cancer patients mitigates the value of ASA physical status categories in predicting which patients are at higher risk for postoperative medical complications. By systematically examining the medical complications of total laryngectomy, our study has identified previous cardiac disease, diabetes, previous stroke, and physical findings of pulmonary wheezing and cardiac murmur as significant preanesthetic risk factors in this population. Although there are important physiologic differences among the types of murmurs, their presence is an indicator of potential cardiovascular complications. Particular attention should be applied to these categories of risk factors in the preoperative history, physical examination, and postoperative care of total laryngectomy patients.

Thorough risk factor assessment preoperatively assured prompt recognition and management of medical complications in this series. Despite life-threatening medical complications in our high-risk population, effective management of these problems resulted in a low mortality. In our institution, a designated medical consultant experienced in the specific medical risk factors and complications of

TABLE 7. PREANESTHETIC RISK FACTORS AND POSTOPERATIVE COMPLICATIONS OCCURRING SIGNIFICANTLY MORE FREQUENTLY (P<.05) IN PATIENTS WITH THOSE RISK FACTORS

Risk Factor	*Complications*
History	
Angina	Pulmonary edema, cardiac arrhythmia requiring therapy
Diabetes mellitus	Stroke, pharyngocutaneous fistula
Severe chronic obstructive pulmonary disease	Pulmonary edema, mechanical ventilation, chronic obstructive pulmonary disease exacerbation
Congestive heart failure	Myocardial infarction, pulmonary edema, cardiac arrhythmia requiring therapy
Stroke	Death, chronic obstructive pulmonary disease exacerbation
Physical examination	
Significant heart murmur	Death, pulmonary edema, chronic obstructive pulmonary disease exacerbation
Pulmonary wheezing	Pulmonary edema, mechanical ventilation
Tests	
Abnormal electrocardiogram	Pulmonary edema

TABLE 8. PREANESTHETIC RISK FACTORS AND COMPLICATIONS ACCORDING TO AGE IN 384 TOTAL LARYNGECTOMIES

	No. of Patients	
	≥65 yr (n=172)	*<65 yr (n=212)*
Risk factors found on history		
Chronic obstructive pulmonary disease	116	144
Hypertension	69	64
Angina	33	28
Myocardial infarction	29	24
Diabetes mellitus	22	19
Severe chronic obstructive pulmonary disease	116	114
Congestive heart failure*	23	9
Stroke	12	10
Liver disease	7	7
Kidney disease	3	2
Risk factors found on physical examination		
Significant heart murmur	20	12
Pulmonary wheezing	7	3
Carotid bruit	6	1
Third heart sound	2	1
Distension of jugular vein	1	0
Risk factors found on tests		
Abnormal electrocardiogram	76	57
Abnormal chest radiograph	35	21
Death*	5	0
Medical complications		
Mechanical ventilation	9	3
Stroke	5	2
Myocardial infarction	1	2
Pulmonary embolus	1	1
Chronic obstructive pulmonary disease exacerbation	19	14
Pneumonia	18	11
Pulmonary edema*	18	3
Cardiac arrhythmia requiring therapy	8	9
Confusion	11	5
Angina	7	4
Urinary obstruction	7	2
Surgical complications		
Pharyngeal fistula	19	29
Postoperative hemorrhage	0	7
Carotid erosion	0	1
Chyle fistula	1	0
Wound infection	18	34

Average postoperative hospitalization was 14.0 days in patients ≥65 yr and 14.9 days in patients <65 yr.

*p<.05.

head and neck cancer patients is a vital member of the head and neck oncology team.

CONCLUSIONS

1. Medical complications are a significant cause of morbidity in total laryngectomy that may result in death, permanent sequelae, or prolonged hospitalization.

2. Total laryngectomy patients experience primarily cardiac and pulmonary complications, not general medical complications such as sepsis and renal failure as experienced by patients of other surgical specialties.

3. Total laryngectomy is as well tolerated by the elderly as by younger patients. Elderly patients do not experience more frequent or more severe medical complications than younger patients. Thus, advanced age is not a medical contraindication to total laryngectomy.

4. Specific risk factor assessment focusing on cardiac and pulmonary disease, and not general ASA physical status, is useful in predicting which patients are at risk for postoperative medical morbidity of total laryngectomy.

5. A medical consultant familiar with the specific risk factors most relevant for head and neck cancer patients is important in assuring that effective internal medicine backup is available in high-risk situations.

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Ann Otol Rhinol Laryngol 99:1990

EXTRALUMINAL ARYTENOID RECONSTRUCTION: LARYNGEAL FRAMEWORK SURGERY APPLIED TO A PEDIATRIC PROBLEM

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Laryngeal framework surgery has proved to be an important alternative in the treatment of vocal cord paralysis in adults. We have modified one of these operations in order to manage debilitating aspiration in a 14-year-old boy. His laryngeal incompetence resulted from a severe neurologic injury and laryngeal scarring from a unilateral arytenoidectomy and multiple Teflon injections. To help him, we studied a series of pediatric larynges and devised an operation that succeeded in rebuilding the bulk of his excised arytenoid cartilage and markedly reducing aspiration.

KEY WORDS — arytenoidectomy, aspiration, laryngeal framework surgery, laryngeal reconstruction, pediatric otolaryngology, phonosurgery, vocal cord injection, vocal cord paralysis.

INTRODUCTION

In the management of vocal cord paralysis, operative procedures seek to restore voice and laryngeal competence without compromising the airway. Teflon injection under local anesthesia has gained wide acceptance in the rehabilitation of adults with unilateral vocal cord paralysis, and arytenoidectomy is used to improve respiratory function in bilateral paralysis.[1,2] While both of these procedures have been applied in children,[3,4] careful consideration is warranted before either is attempted. It is much more difficult to achieve an acceptable result in a child, as the laryngeal lumen is smaller and the procedures must be performed under general anesthesia without immediate patient feedback to determine the optimum amount of correction. Further, children with vocal cord paralysis frequently suffer from complex neurologic disease affecting cranial nerves other than the vagus as well as central nervous system function.[5,6]

The treatment of the malfunctioning larynx in childhood would be enhanced by the development of operations that could be adjusted intraoperatively and could be reversed in case the initial estimate of needed correction subsequently proved inaccurate or the patient's condition improved.

Isshiki thyroplasty type I, a laryngeal framework operation designed to medialize the unilaterally paralyzed vocal cord, has been applied in the adult population with considerable success.[7-10] It would satisfy the conditions of adjustability and reversibility that are desirable in treating children.[11] In this operation, the vocal cord is medialized by depressing an overlying window of thyroid cartilage that is secured with a rectangular Silastic block. The operation depends on a knowledge of the relationship between external laryngeal landmarks and endolaryngeal structures (ie, location of true vocal cord). That such relationships have not been worked out in the growing larynx of the child limits the application of this valuable procedure in this age group. The possibility of manipulating other parts of the endolarynx to improve the respiratory or sphincteric functions of the larynx in childhood is intriguing as well.

A child with complex neurologic disease and intractable aspiration following multiple Teflon injections and a unilateral arytenoidectomy presented to Children's Hospital of Pittsburgh. In order to treat his laryngeal disease, the necessary parameters for laryngeal framework operation were studied in a series of pediatric larynges and an operation to replace the bulk of his excised arytenoid cartilage was devised.

METHODS AND MATERIALS

Ten formalin-fixed larynges obtained at autopsy were studied, with an age range of 10 days to 16 years. All of the subjects whose larynges were measured had a history of normal growth and development and were free of aerodigestive anomalies. In each larynx, the level of the true vocal cord and the position of the center of the base of the arytenoid were determined relative to external landmarks on the thyroid lamina. These determinations were made by passing a pin through the vocal cord and the cricoarytenoid joint, respectively, from the laryngeal lumen to the outer surface of the thyroid lamina; the position of the pin was measured with calipers. In addition, the angle of inclination of the posterior cricoid cartilage relative to the vocal cord was calculated and the height of the arytenoid measured.

In designing the operation for arytenoid recon-

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Presented at the meeting of the American Broncho-Esophagological Association, Palm Beach, Florida, May 2-3, 1990.

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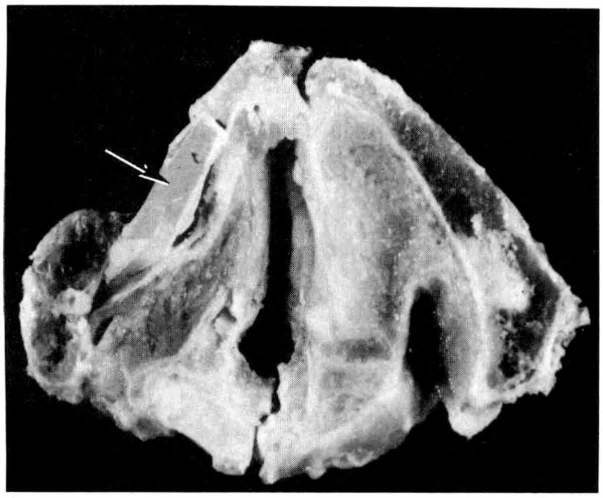

Fig 1. Transverse gross section of cadaver larynx. Extraluminal arytenoid reconstruction replaces excised left arytenoid. This prothesis (arrow) is too small to close posterior gap.

struction, both sides of three larynges were used. The arytenoid cartilages were removed in the manner of the Woodman procedure.[2] Silastic blocks of various sizes were inserted after depressing and scoring a window of thyroid cartilage. The effect on the posterior glottis was observed and the configuration that best replaced the bulk of the arytenoid without compromising the laryngeal lumen was selected. The larynx was then frozen at −20°C and sectioned on a bandsaw to observe the effect on the laryngeal cross section (Fig 1).

RESULTS

Measurement of the positions of cartilages and soft tissues in a small larynx are necessarily inexact. Still, several useful observations can be made.

1. Throughout childhood, as in the adult, the level of the upper edge of the true vocal cord is consistently located one half of the distance between the thyroid notch and the base of the thyroid cartilage in the midline (anterior thyroid height; Fig 2). A line bisecting and at right angles to the anterior thyroid height identifies the level of the upper edge of the true cord (thyroid width; Fig 2).

2. At all ages the center of the base of the arytenoid cartilage is located at the junction of the anterior two thirds and posterior one third of the thyroid width.

3. The angle of inclination of the superior surface of the cricoid cartilage is approximately 30° relative to the true cord (and thus the thyroid width) in all age groups.

4. The height of the arytenoid cartilage throughout childhood measures approximately two thirds of the anterior thyroid height.

With these measurements as a guide the following procedure was devised.

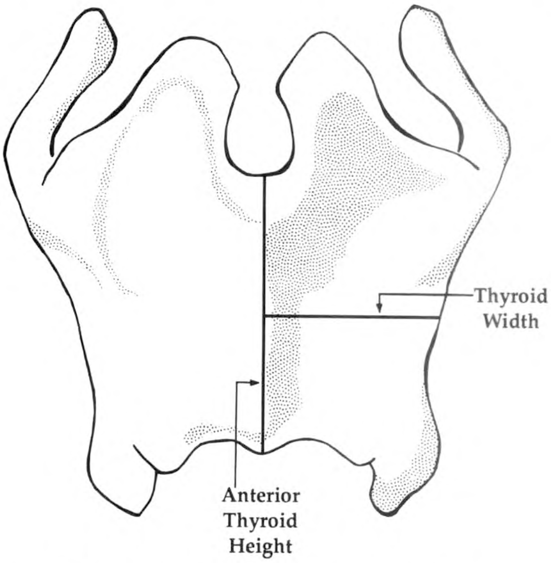

Fig 2. Anterior thyroid height and thyroid width.

1. Through a transverse cervical incision located at the thyroid notch, the thyroid laminae are exposed, with the outer perichondrium left attached.

2. The anterior thyroid height is defined and bisected.

3. A window of thyroid cartilage is designed (Fig 3A). Its anterior limit is a few millimeters posterior to the midline and its posterior inclination of 30° begins at the midpoint of the thyroid width. The posterior angled portion, overlying the posterior glottis, should be one half the anterior thyroid height in the vertical dimension and should stop a few millimeters short of the edge of the thyroid ala to maintain cartilaginous support.

4. The window is first scored vertically to allow the cartilage to bend and then outlined with a Freer septal D knife. Care must be taken not to penetrate the inner perichondrium.

5. The inner perichondrium is then separated from the thyroid lamina surrounding the window with a Woodman elevator. This elevation allows the window of cartilage to be depressed while leaving the perichondrium attached to its inner surface (Fig 3B).

6. A prosthesis is carved from a medical-grade Silastic block of medium hardness (Fig 4). Its lateral surface is cut to fit the cartilage window. A four-sided pyramid is carved from the posterior portion on the medial surface to simulate the arytenoid cartilage. Its anterior extension medializes the posterior vocal cord remnant.

7. The Silastic prosthesis is used to depress the scored cartilage window and is secured in position with permanent, monofilament sutures (Fig 3C). The wound is not drained. Figure 5 shows the final result.

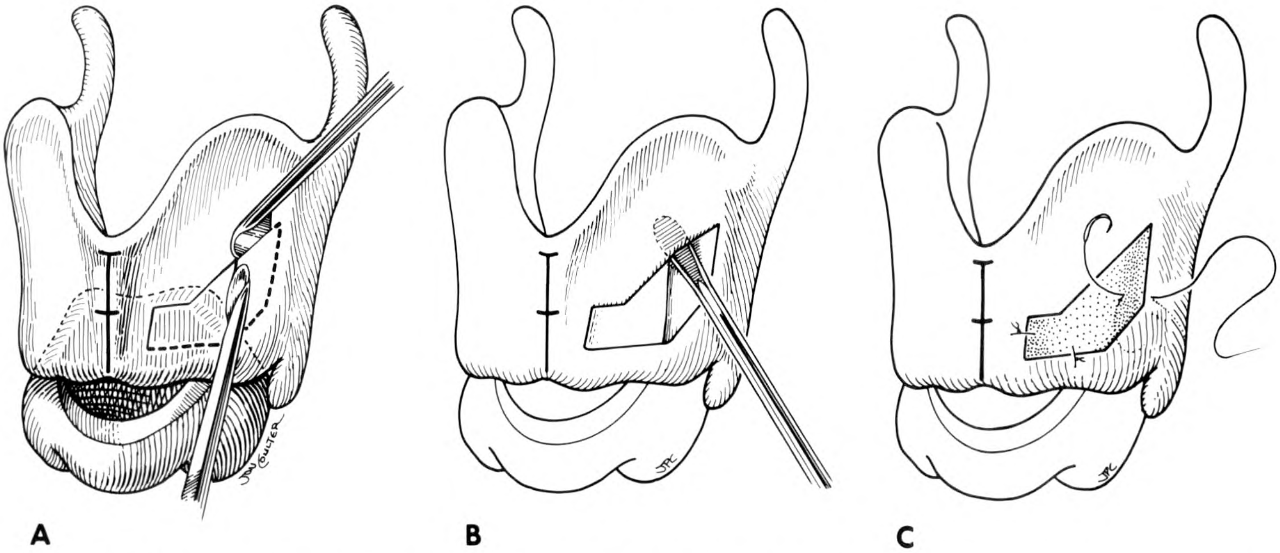

Fig 3. Procedure. A) Cartilage window is marked, then scored vertically. Cartilage is then incised with care not to penetrate inner perichondrium. B) Cartilage window is depressed by elevating inner perichondrium. C) Prosthesis is secured with permanent, monofilament sutures.

CASE REPORT

The patient is a 14-year-old boy who sustained a severe closed-head injury in a motor vehicle accident at age 4 that left him with bilateral hemiparesis, a severe seizure disorder, hydrocephalus treated with a ventriculoperitoneal shunt, and a left vocal cord paralysis. He was chronically tracheotomized for 5 years, then successfully decannulated at age 9. He underwent a Teflon injection of his left vocal cord 2 years later to improve his very weak voice. Several weeks following this injection he developed stridor and required replacement of his tracheotomy. Subsequently, a left arytenoidectomy and cricopharyngeal myotomy were undertaken to improve his swallowing and allow decannulation. Severe aspiration ensued that could not be improved by Teflon injection of the posterior glottis or removal of the tracheotomy tube, and a gastrostomy tube was inserted. The patient lived for a full year with no oral feedings. Yet another Teflon injection was offered, but the family declined, and he was then evaluated at the Children's Hospital of Pittsburgh.

On examination the boy was cachectic, wheelchair-bound, and contorted from his hemiparesis. Mirror examination of the larynx demonstrated a large posterior glottic gap and pooling of secretions. The gag reflex was absent. At direct laryngoscopy a lateralized left vocal cord, a large posterior glottic gap, and poor mobility of the right true cord were noted. Laryngeal electromyography demonstrated innervation of the right vocalis muscle, and palpation showed right cricoarytenoid mobility to be moderately impaired. A tracheotomy was performed and injection of the left posterior part of the glottis with Gelfoam was attempted. The larynx was too densely scarred for Gelfoam to be injected.

The boy continued to be unable to swallow solids or liquids without gross aspiration and was aphonic. The possibility of modifying Isshiki thyroplasty type I to narrow the posterior glottis was presented to the family. They agreed and the previously described cadaver experiments were undertaken to devise the necessary procedure.

A series of Silastic prostheses were constructed of various thicknesses. At operation the various blocks were inserted and the effects monitored by endoscopy (Fig 6). The patient recovered quickly from the procedure. Intensive swallowing therapy was instituted and a Passy-Muir valve fitted to his tracheotomy. Over the ensuing 3 weeks he gradually became able to swallow solids and semisolids, but was still noted to aspirate liquids on modified barium swallow study. He was discharged to continue therapy at home.

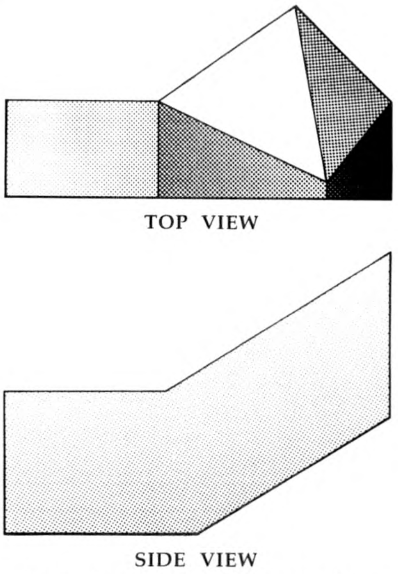

Fig 4. Design of Silastic prosthesis.

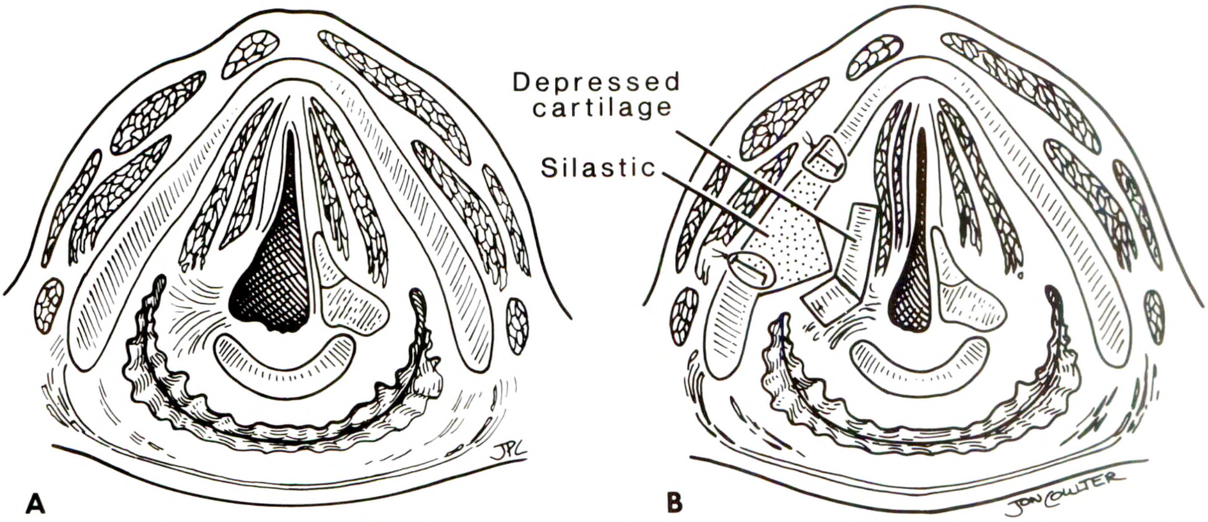

Fig 5. Transverse sections of larynx. A) Effects of arytenoidectomy on posterior glottis. B) Prosthesis depressing window of vertically scored cartilage and narrowing posterior glottic gap.

At 6-month follow-up, the patient's voice was noted to be weaker. He returned to Pittsburgh, where endoscopy confirmed a small increase in his posterior glottic gap. Rather than revising his open procedure, we injected Teflon between the window of cartilage and the Silastic prosthesis, modestly increasing the bulk of the prosthesis. This fine tuning improved the narrowing of the glottic gap. He noticed an immediate increase in vocal strength and was finally able to swallow carbonated beverages without aspiration.

At 1-year follow-up his laryngeal repair remains intact and he has gained 13.5 kg (30 lb). He no longer requires gastrostomy feedings, but his tracheotomy remains in place.

DISCUSSION

The concept that the function of the larynx could best be preserved by not entering its lumen during surgical manipulations is one of the fundamental principles of the new phonosurgical procedures pioneered by Nobuhiko Isshiki. He described a series of operations designed to alter the mass and tension of the true vocal fold by manipulation of the laryngeal framework and thus improve phonatory function.[7,8,12,13] While the durability of some of these operations remains to be established, their effectiveness in altering voice quality and lack of adverse effect on airway patency and laryngeal function seem clear.

The possibility of applying the principles of laryngeal framework surgery to improve the respiratory and protective functions of the larynx is appealing. Further, when designing operations for children it is important to account for the future growth of organs and the potential for improvement in even chronic conditions. Thus, scarring should be avoided and options for reversing or modifying the procedure are desirable.

The growth of the larynx in relation to somatic growth, as well as the growth of the laryngeal components, has been well studied.[14,15] In general, growth of the overall dimensions of the larynx is proportional to growth of the crown-heel length (somatic height), with growth spurts between birth and 3 years and again at puberty. Growth of the laryngeal components (ie, cartilages and soft tissues) is proportional throughout childhood, although there are marked alterations in shape, particularly of the epiglottis and thyroid laminae. Thus, although the larynx changes greatly during childhood, the measurement of external dimensions should continue to give useful information about the position and size of endolaryngeal structures.

This supposition has been confirmed by the present study. Measurement of the anterior thyroid height and the thyroid width can be used to accu-

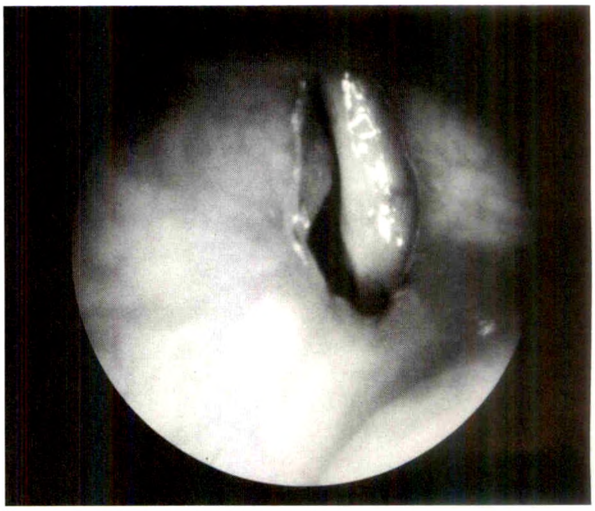

Fig 6. Postoperative endoscopic view of larynx from reported case. Bulk of previously excised left arytenoid is restored. Small posterior glottic gap remains.

rately predict the location of the true vocal cord and arytenoid throughout childhood.

The ability to recreate the bulk of the arytenoid should not encourage otolaryngologists to perform arytenoidectomy without careful consideration, especially in children. Should an arytenoidectomy result in an excessively patent posterior glottis, however, extraluminal arytenoid reconstruction provides a way to manipulate the glottis despite the presence of endolaryngeal scarring. Intraoperative endoscopic assessment helps in choosing a prosthesis that will narrow the posterior glottic gap without impinging on the airway.

It should be pointed out that although Isshiki thyroplasty type I can be performed relatively safely in adults without the use of a tracheotomy, the patient described in this report was chronically tracheotomized because of impaired mobility of the contralateral vocal cord. We have no experience with doing this procedure without initial airway protection. Further, while intraluminal extrusion of Silastic has not been reported with Isshiki thyroplasty and did not occur in our patient, it is a theoretic risk of using a large piece of prosthetic material.

Laryngeal framework surgery is gaining increasing acceptance in the treatment of functional laryngeal problems in adults. Study of laryngeal growth may help extend the usefulness of these new procedures to the treatment of injured and neurologically impaired children.

ACKNOWLEDGMENTS — The author thanks Drs Charles D. Bluestone, Sylvan E. Stool, and Margaretha Casselbrant for their help and encouragement with this project.

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PAN AMERICAN ASSOCIATION OF OTORHINOLARYNGOLOGY–HEAD AND NECK SURGERY

The XXII Congress of the Pan American Association of Otorhinolaryngology–Head and Neck Surgery will be held December 1-5, 1990, in Buenos Aires, Argentina. For further information, contact Dr Alejandro Terzian, Secretary General, Delfino Turismo SRL, San Martin 427, 1004 Buenos Aires, Argentina; phone 54 1 394-2014/2247/4181, FAX 54 1 111595/54 1 3945379.

Ann Otol Rhinol Laryngol 99:1990

SEVERE UPPER AIRWAY OBSTRUCTION IN CHILDREN SECONDARY TO LINGUAL TONSIL HYPERTROPHY

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Lingual tonsil hypertrophy in children is a rarely reported disorder. Two cases of severe upper airway obstruction in pediatric patients secondary to marked lingual tonsil enlargement are reported. Both children were effectively treated with lingual tonsillectomy. The surgical technique, using an insulated Bovie tip, is described.

KEY WORDS — lingual tonsils, stricture, upper airway obstruction.

INTRODUCTION

Hypertrophy of the adenoid and palatine tonsils is a well-recognized cause of chronic upper airway obstruction in children.[1] Inflammation of these tissues may also lead to significant acute upper airway obstruction.[2] It is for the most part unrecognized that the lingual tonsils may be the cause of both acute and chronic obstruction in pediatric patients. In this paper, we report two cases of severe upper airway obstruction secondary to lingual tonsil enlargement in children. The limited literature regarding lingual tonsil hypertrophy leading to airway obstruction is also reviewed, and recommendations regarding the management of these patients are made.

CASE REPORTS

Case 1. A 9-year-old boy with Down syndrome presented to the emergency room with acute stridor. At bedtime he had been breathing normally, but 2 hours later he was found sitting leaning forward, stridorous, and in moderate distress. The past medical history was remarkable for multiple episodes of "croup" managed by outpatient treatment at another institution and an adenotonsillectomy at age 7. The patient was combative and anxious, with severe inspiratory stridor. His vital signs revealed a temperature of 38°C orally, a pulse of 160 beats per minute, and a respiratory rate of 36 breaths per minute. A capillary blood gas measurement revealed a pH of 7.27, a carbon dioxide of 57, and a P_{O2} of 56. After immediate transport to the operating room, inhalation anesthesia was induced during spontaneous respiration, and laryngoscopy was performed. Extremely hypertrophic lingual tonsil tissue was noted, extending into the valleculae and displacing the epiglottis posteriorly and producing a near-total obstruction of the glottis. The epiglottis and larynx were normal. A rigid ventilating bronchoscope was passed, and muscle relaxants were administered. After examination of the trachea and bronchi, the bronchoscope was exchanged for an endotracheal tube. Specimens for culture and biopsy were taken, and the patient was transferred to the pediatric intensive care unit.

Intravenous ampicillin sodium and dexamethasone sodium phosphate were given every 6 hours, and the patient was extubated after 48 hours. The blood cultures and Monospot test on blood drawn on admission were negative for pathogens. The biopsy showed nonspecific inflammation, and the surface cultures grew multiple organisms. Results of a thyroid scan were normal, and flexible fiberoptic endoscopy confirmed the presence of markedly hypertrophic lingual tonsils.

The patient was discharged after 5 days and returned for lingual tonsillectomy 3 weeks later. A nasotracheal tube was inserted after the induction of general anesthesia. Insertion of the tube was more difficult than usual because of the markedly enlarged lingual tonsils. A Jennings mouth gag, a 3-0 silk traction suture through the tongue, and a Weeder tongue depressor provided excellent exposure of the huge lingual tonsils (Fig 1A). The lingual tonsils were removed by grasping the tissue with a curved Allis clamp and cutting just above the fascia at the base of the tongue. An insulated Bovie tip with the electrocautery unit set on coagulation was used as a cutting instrument (Fig 1B). A Yankauer suction tip was used to evacuate smoke during the procedure. Blood loss was minimal.

Following the removal of a $1\frac{1}{2} \times 2 \times 3$-cm mass of lingual tonsil, the airway was clearly unobstructed (Fig 1C,D). The patient recovered uneventfully, and he has had no further episodes of airway obstruction in the 18 months following the operation.

Case 2. A 5-year-old boy was referred for evaluation of obstructive sleep apnea. His parents described a lifetime history of daytime mouth breathing and sleep disturbances with loud snoring, com-

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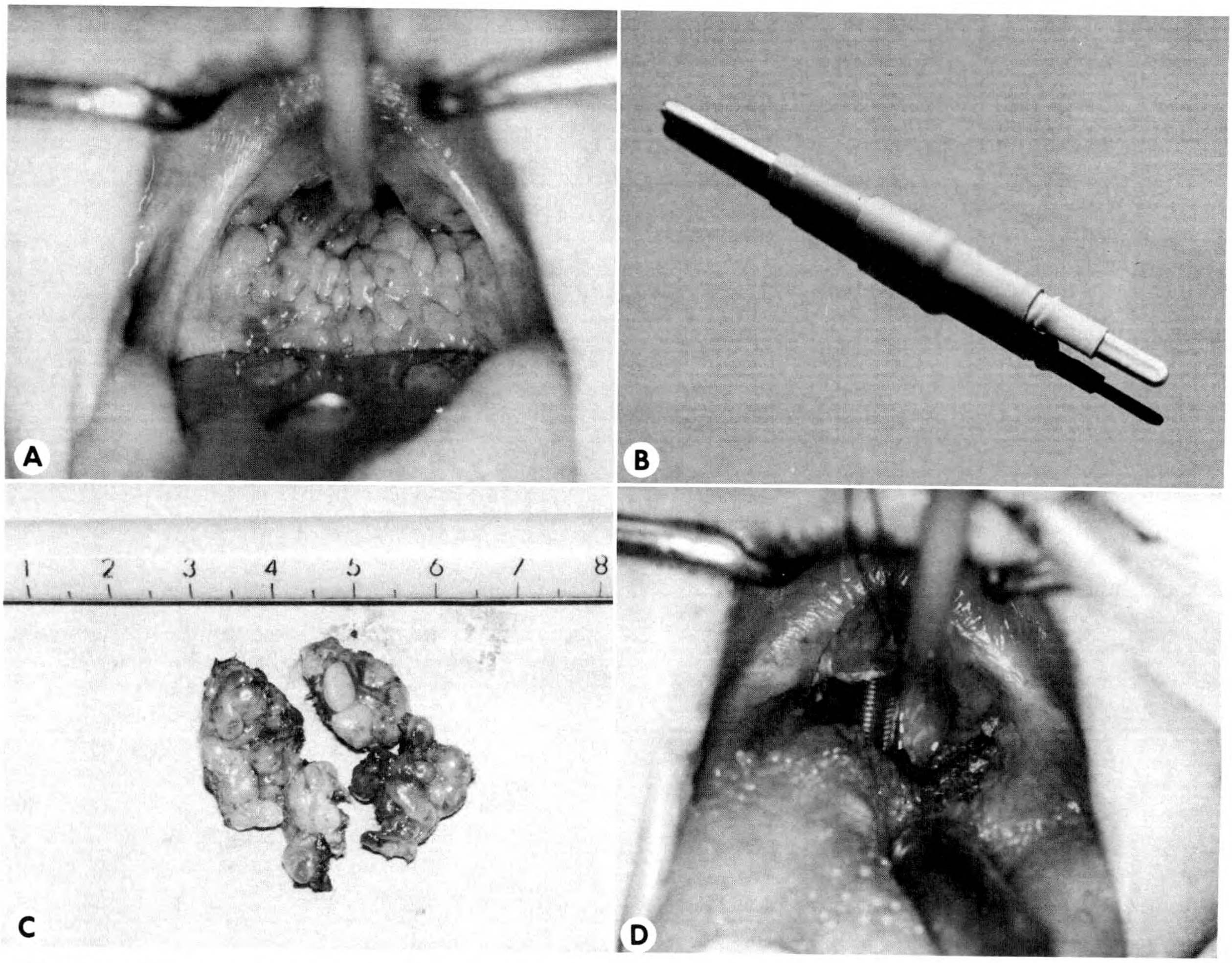

Fig 1. (Case 1) A) Large obstructing lingual tonsils. B) Insulated Bovie tip used for lingual tonsillectomy. C) Mass of lingual tonsil tissue ($1\frac{1}{2}$ x 2 x 3 cm) removed. D) Airway following removal of lingual tonsils.

plete obstruction with sternal retractions, and orthopnea. They specifically noted that he was unable to sleep without being propped up with at least two pillows. Examination revealed mouth breathing and hyponasal speech. His palatine tonsils were moderate in size and nonobstructing. Flexible fiberoptic endoscopy revealed only a moderately enlarged adenoid pad. Huge lingual tonsils, producing near-total obstruction of the hypopharynx, were also noted (Fig 2A).

The patient returned for adenoidectomy and lingual tonsillectomy a few weeks later. Significant difficulty in maintaining mask ventilation was encountered during the induction of general anesthesia. Nasotracheal intubation was also difficult, because the extremely enlarged lingual tonsils totally obscured the epiglottis and glottis (Fig 2B). A 2 x $2\frac{1}{2}$ x 4-cm lingual tonsil pad was removed with an insulated Bovie tip (Fig 2C). The previously obstructed laryngeal structures were immediately visible (Fig 2D). The nasotracheal tube was then exchanged for an orotracheal tube, and a routine adenoidectomy was performed.

The patient has been followed up for 6 months postoperatively and is completely relieved of his symptoms. He is now able to sleep lying flat. Flexible fiberoptic examination of the larynx revealed excellent healing and a widely patent hypopharynx with clearly visible supraglottic and glottic structures (Fig 2E).

DISCUSSION

Hypertrophy of the adenoid and palatine tonsils has been implicated in a spectrum of severe and even life-threatening upper airway disease. Attention has been focused on its role in obstructive sleep apnea in adults and in children and the efficacy of adenotonsillectomy in eliminating or significantly reducing the severity of symptoms.[3] The lingual tonsils, however, are for the most part neglected in studies of these topics. Lingual tonsil enlargement most commonly produces symptoms of pain, dysphagia, otalgia, or the sensation of a lump in the throat; and occasional reports of lingual tonsillectomy for these complaints may be found.[4] Only a few reports focus on airway symptoms caused by lingual tonsils. Joseph et al[4] reported on lingual tonsillectomy performed in 11 patients, most with symptoms of dysphagia or recurrent infection; one

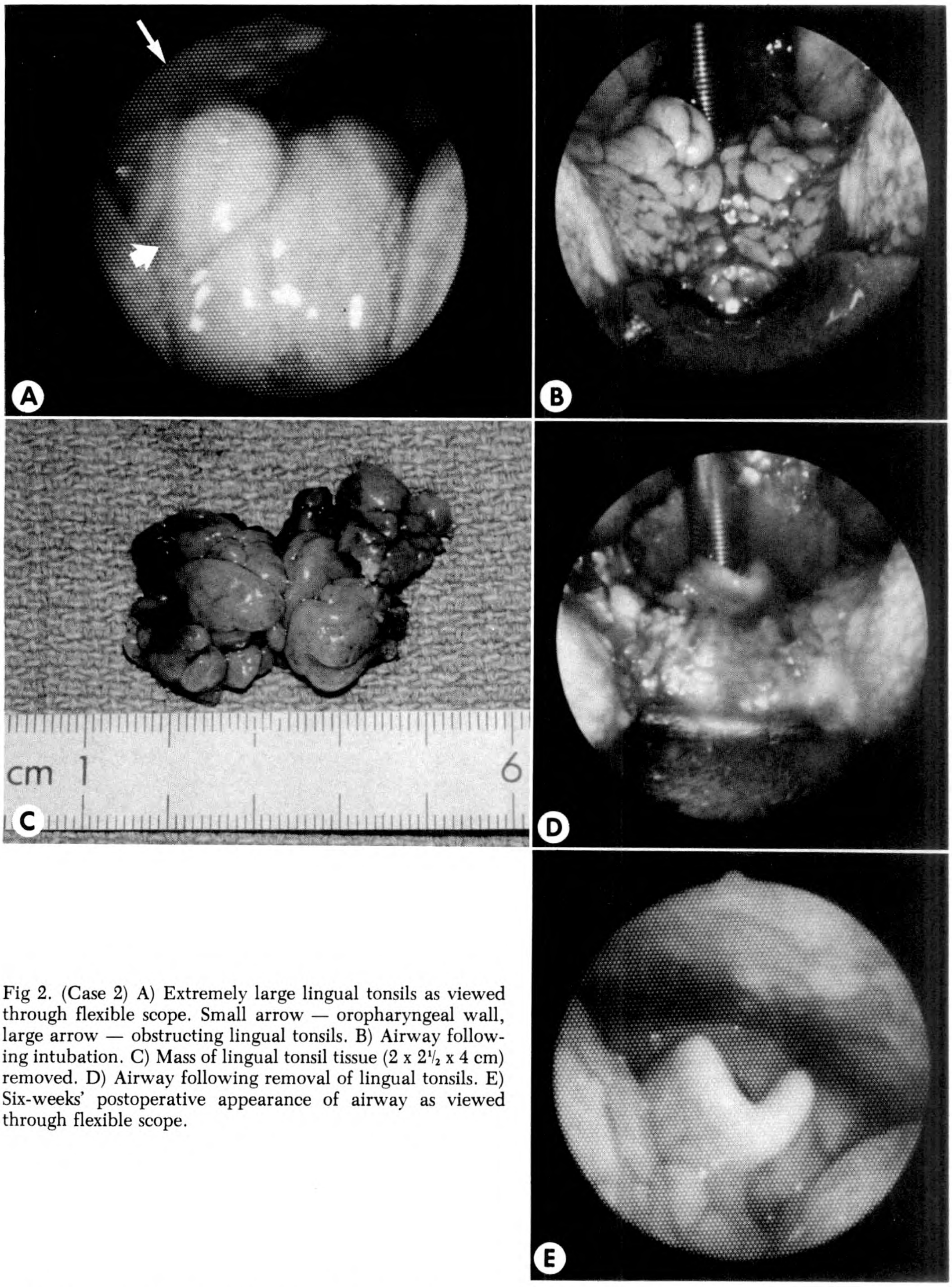

Fig 2. (Case 2) A) Extremely large lingual tonsils as viewed through flexible scope. Small arrow — oropharyngeal wall, large arrow — obstructing lingual tonsils. B) Airway following intubation. C) Mass of lingual tonsil tissue (2 x $2^1/_2$ x 4 cm) removed. D) Airway following removal of lingual tonsils. E) Six-weeks' postoperative appearance of airway as viewed through flexible scope.

adult patient presented with stridor and sleep disturbances that resolved after tonsillectomy. Olsen et al[5] described a case of a 13-year-old boy with obstructive sleep apnea relieved by lingual tonsillectomy. Johnson et al[6] reported an adult patient with acute purulent lingual tonsillitis and bleeding from this area who developed complete airway obstruction during induction of general anesthesia, necessitating an emergency tracheotomy. Medical treatment allowed decannulation; no further treatment was described.

The patient in case 1 developed acute upper airway obstruction secondary to sudden inflammation of his chronically enlarged lingual tonsils. This is the first report of a pediatric patient developing life-threatening obstruction secondary to a lingual tonsil disorder. His recurrent episodes of "croup," most likely due to recurrent lingual tonsillitis with airway compromise, resolved after lingual tonsillectomy. Prior adenotonsillectomy had not relieved his symptoms, and in fact it has been noted by various authors that lingual tonsil disease is noted most commonly in patients who have undergone tonsillectomy.[7] Whether this anecdotal finding represents compensatory hypertrophy or a general predisposition to growth of tonsil tissue is unknown.

The child in case 2 had classic obstructive apnea secondary to chronically enlarged lingual tonsils. Although no sleep studies were performed, the history and physical findings clearly confirmed the diagnosis. The flexible fiberoptic scope is extremely useful in evaluating patients with obstruction symptoms, and in case 2 the diagnosis was made with this instrument. On the basis of the literature reviewed for this report, obstructive sleep apnea in children secondary to lingual tonsil hypertrophy is rare. Only two other case reports were located in a 20-year retrospective search of the literature.[5,8]

Various techniques for removing the lingual tonsils have been proposed. Dissection and snare, adenoid curettes, cryosurgery, and the carbon dioxide laser have all been advocated by different authors.[7,9,10] The Bovie electrocautery unit with an insulated tip was used in the patients presented here. With the unit on the coagulation setting, rapid and bloodless dissection was possible. The lingual tonsil tissue was well delineated from the tongue musculature by a clearly evident fascial plane in both children. Nasotracheal intubation, a Jennings mouth gag, a heavy silk retraction suture through the tip of the tongue, and a Weeder tongue depressor aided in exposure. The use of a curved Allis clamp to grasp the lingual tonsils and draw them anteriorly allowed ideal visualization and easy removal.

No difficulties with postoperative swelling were encountered, and the increased airway diameter after lingual tonsil removal greatly outweighed the moderate degree of swelling and edema noted. As a precaution, intravenous dexamethasone sodium phosphate at a dose of 12 mg preoperatively and 6 mg every 6 hours for two doses postoperatively was prescribed for each child. The postoperative course of both patients was similar to that following routine adenotonsillectomy.

SUMMARY

In summary, lingual tonsil enlargement may produce severe airway compromise in children. Chronically enlarged tissue may lead to classic obstructive sleep apnea, and acute inflammation may lead to life-threatening obstruction. The routine use of the flexible fiberoptic scope to examine the upper airway in children with obstructive symptoms facilitates clear visualization of the lingual tonsils. Indirect mirror examination is not as useful, as protrusion of the tongue does not allow the examiner to clearly recognize the relative size of the lingual tonsils. The use of the Bovie cautery device with an insulated tip allows a rapid, bloodless, anatomic dissection of the lingual tonsils. Finally, lingual tonsillectomy is a relatively safe and effective procedure in the treatment of upper airway obstruction secondary to lingual tonsil hypertrophy in children.

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Ann Otol Rhinol Laryngol 99:1990

ARYEPIGLOTTIC FOLD EXCISION FOR THE TREATMENT OF SEVERE LARYNGOMALACIA

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Laryngomalacia is the most common laryngeal anomaly. Clinical presentation is most often associated with stridor, which usually resolves spontaneously by the second year of life. Infrequently, laryngomalacia can be severe and cause dyspnea and feeding difficulties. These children require surgical treatment, including tracheostomy. A new procedure has been recently described for the endoscopic excision of the aryepiglottic folds. The authors report results in 39 patients who have been treated with this procedure. One failure required tracheostomy. No recurrence of dyspnea was noticed in the other children. Gastroesophageal reflux, associated with 50% of our cases, was also noted in our only failure. We advocate endoscopic treatment in children with severe laryngomalacia.

KEY WORDS — endoscopic treatment, laryngomalacia.

Laryngomalacia or congenital laryngeal stridor (CLS) is a usually benign condition of infants. The clinical presentation begins with stridor, which is often present from birth and usually resolves spontaneously by the second year of life. About 60% of congenital laryngeal anomalies that presented with stridor are due to laryngomalacia.[1-3]

Infrequently, CLS may have a poor or even fatal outcome due to associated respiratory and swallowing disorders.[3-7] These cases of severe CLS need urgent treatment. Many surgical treatments have been described, including tracheostomy, which is known for its risks in infants.[8] A new endoscopic surgical treatment consisting of excision of tissues in excess of the laryngeal margins has also been described.[9] This paper reports our results with this technique in 39 infants with severe CLS.

MATERIALS AND METHODS

This is a retrospective study consisting of 39 infants referred to our pediatric ear, nose, and throat department from 1985 to 1987 who underwent endoscopic surgical treatment for severe CLS. There were 25 boys and 14 girls with ages ranging from 15 days to 19 months (mean age, 15 weeks) at time of treatment. Criteria for surgical treatment were based on clinical findings.

Clinical Findings. Respiratory difficulties were constant in 37 cases and intermittent in 2 cases. The symptoms included dyspnea with retractions of the neck, chest wall, and upper abdomen. In the most severe cases (3 infants), apnea and cyanosis were noted, and emergency intubation was performed prior to surgical treatment. Respiratory symptoms increased with upper respiratory tract infections or pulmonary infections in 4 cases. In 6 cases dyspnea worsened during feeding. Feeding difficulties were often associated with respiratory disorders. In 3 cases repeated choking with feeding was observed. Failure to thrive was present in 21 cases. Lack of weight gain or even regression was seen in 23 cases.

Diagnosis of gastroesophageal reflux (GER) was made most often a few days or weeks before operation. Barium swallow study and flexible esophageal examination were used when GER was suggested by history and physical examination. Seventeen of our 39 infants certainly had GER, 9 with esophagitis. Another 4 infants were suspected to have GER. Preoperative treatment consisted of positioning, thickening of food, and drugs such as metoclopramide hydrochloride. In patients with esophagitis, we used antacids. In none of the patients did respiratory symptoms improve with antireflux therapy.

Endoscopic Findings. Definitive diagnosis was confirmed by flexible nasolaryngoscopy, with the awake infant in a supine position. Direct laryngoscopy should be performed to rule out synchronous airway anomalies. In 34 cases laryngomalacia was global, while in 5 cases it was limited to the posterior margin. Interestingly, these 5 were the infants with most severe dyspnea. Four of these 5 infants had significant GER with esophagitis. In every case mucosal edema was present, sometimes with redundant mucosa. Dynamic observation showed laryngeal inlet retraction obstructing the glottis.

Surgical Treatment. The procedure was performed with general anesthesia and orotracheal intubation. A standard microlaryngoscopic technique was used with microscissors and microforceps. Electrocautery was used as necessary.

In 35 cases we used a variant of the technique de-

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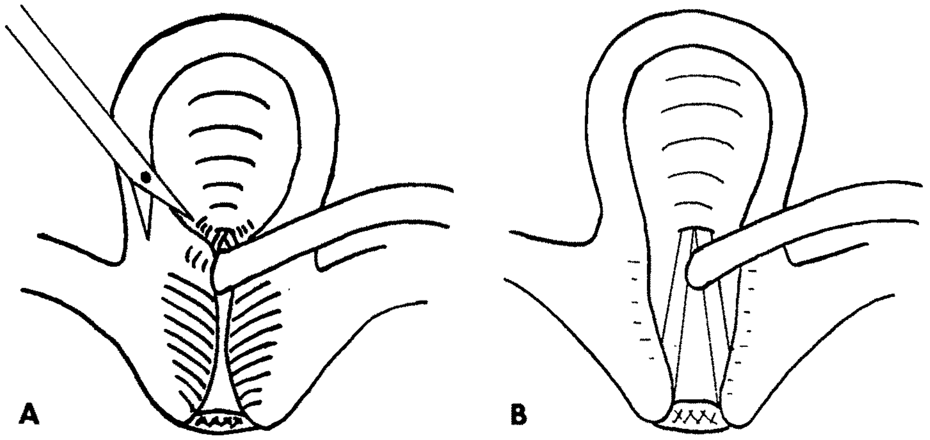

Suction test. A) Preexcision, to determine amount of tissue to be trimmed. B) Postexcision.

scribed by Lane et al[9] in 1984, which consists of excision of excess tissue of the laryngeal margins. We performed a "suction test" by introducing an aspiration cannula in the laryngeal inlet in order to reproduce the collapse of the laryngeal margin that happens with CLS during inspiration. In this way the anatomy of the collapse can be determined and the amount of tissue to be trimmed can be precisely ascertained (see Figure, A). A repeat suction test after excision confirms that the margin is no longer collapsing and the glottis remains spontaneously visible (see Figure, B). Generally, the excess mucosa was found to be on the aryepiglottic fold and the arytenoid cartilages. In 13 cases the excision was extended to the lateral edges of the epiglottis.

Another technique, described by Seid et al,[10] which consists of a division of the aryepiglottic folds to lengthen the laryngeal inlet in the anteroposterior axis, was used in three patients.

A technique described by Solomons and Prescott[11] was used in one patient. This involves a resection of the aryepiglottic folds along with a glossoepiglottopexy.

Postoperative Treatment. All patients received postoperative antibiotics (penicillin and metronidazole) and corticosteroids such as dexamethasone. In the 21 cases in which GER was documented, we used the same antireflux therapy as described preoperatively.

Follow-up Endoscopy. Thirty patients underwent follow-up laryngoscopy between 1 and 6 months after the procedure. None had any further inspiratory retraction of the laryngeal margins.

RESULTS

None of the 39 infants died as a result of the operation or respiratory problems (one death occurred elsewhere secondary to an unrelated neurologic disorder). In 30 cases immediate and complete relief of the respiratory symptoms allowed extubation in the operating room. No recurrence of dyspnea was noted. The infants were hospitalized postoperatively with close monitoring for 48 hours.

There were three cases of postoperative complications requiring intubation after the procedure. One patient had a postoperative hemorrhage. Two patients had dyspnea related to secondary mucosal edema. Duration of intubation secondary to postoperative complications ranged from 12 hours to 7 days (one child was intubated for 15 days for associated bronchiolitis).

Failures. There were two patients who had transient failure. One could not be extubated because of persistent dyspnea, and the other child still had dyspnea 15 days after the initial procedure. Both of these patients had had simple division of the aryepiglottic folds. The revision operation consisted of excision of the excess tissue of the aryepiglottic folds, and both these patients had uneventful postoperative recoveries following the revision.

Only one patient had complete failure. This infant had two separate procedures, with excision of excess tissue of the laryngeal margin. Despite careful postoperative management, he had significant edema of the arytenoids that made extubation unfeasible, and he required tracheostomy for 6 months. Gastroesophageal reflux was a significant problem in this child and necessitated gastric fundoplication.

Feeding Difficulties. All the infants who had preoperative feeding difficulties secondary to dyspnea improved quickly after treatment. One child continued to choke frequently during feedings for about 3 months postoperatively. All the infants made significant progress in gaining weight (up to 1 kg in 20 days).

Stridor. Stridor disappeared in 31 cases; however, in three patients transient stridor recurred with pharyngitis. In seven children stridor was heard only when the child was crying or asleep. In one case stridor persisted permanently.

The length of postoperative hospitalization has shortened with our growing experience. Children are generally discharged 2 days after the procedure if postoperative recovery is uneventful.

DISCUSSION

The severity of laryngomalacia is determined by the degree of respiratory distress and associated feeding difficulties. In its severest form some type of airway intervention is required to relieve dyspnea and failure to thrive. Tracheostomy has well-recognized risks in young infants; therefore, other treatments for severe CLS have been sought. Hyomandibulopexy has been abandoned, since it was not always successful.[7]

Direct surgical attack of the obstructing lesion was first suggested by Variot[12] in 1898 in the form of resection of the excess of mucosa of the aryepiglottic folds; however, he did not perform this operation. In 1907, Reardon[13] pursued a similar idea; however, initial attempts had to await the advent of suspension laryngoscopy. Iglauer[14] endoscopically resected the free part of the epiglottis in 1922. This method was also used by Schwartz[8] in 1944. Ochs[15] in 1958 described lingual tonsillectomy and resection of the mucosa of the lingual aspect of the epiglottis. These surgical techniques have been abandoned.

In 1928, Hasslinger[16] was the first to report two cases of successful endoscopic resection of the aryepiglottic folds. In 1984, Lane et al[9] presented a case report of trimming of the arytenoid process under microlaryngoscopy. In 1987, Zalzal et al[17] reported 10 cases of excision of redundant mucosa over the margins of the larynx for CLS, with good results. Our technique is similar, but modified by the use of the "suction test," which specifically localizes the area and amount of tissue to be excised. In this way we obtained good postoperative results in 37 patients. We did not find endoscopic division of the aryepiglottic folds as described by Seid et al[10] to be successful, since we had to reoperate on two of the three infants treated in this way. The only time associated epiglottopexy was effective was when it was done in conjunction with excision of aryepiglottic folds.

On the basis of the excellent results obtained, we advocate endoscopic resection of the aryepiglottic folds as an effective treatment of laryngomalacia with severe laryngeal dyspnea. The clinical criteria for operation must be ascertained by laryngotracheoscopy in order to rule out other glottic, subglottic, or tracheal anomalies and to evaluate the amount of inspiratory occlusion of the laryngeal inlet.

An important finding in our series was the association of GER with 50% of our cases. In the most severe cases it was always present. We think our only failure was related to major GER that made tracheostomy unavoidable.

Thus, a diagnostic evaluation for GER with a barium esophagram or pH studies is an important aspect of the preoperative assessment of children with severe CLS. Treatment of GER should be started before surgical correction of CLS is undertaken whenever possible.

CONCLUSION

Endoscopic resection of redundant mucosa of the laryngeal margin is an effective treatment of severe laryngomalacia. This procedure is an improvement over previous treatments. Our "suction test" is a dependable guide for the amount and localization of tissue to be trimmed. Before surgical treatment for CLS is performed, GER should be looked for and treated if present.

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RESPONSES TO RUBELLA, TETANUS, AND DIPHTHERIA VACCINES IN OTITIS-PRONE AND NON-OTITIS-PRONE CHILDREN

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Delayed immunologic maturation — among other things based on a selective lack of antibodies against some acute purulent otitis media (AOM)-associated pneumococcal types — has been proposed in children with recurrent AOM (rAOM). To further elucidate the immunologic response in these children, we compared the antibody responses to diphtheria, tetanus, and rubella vaccinations in 13 children with rAOM and 29 children without AOM. The children took part in a prospective study from birth to the age of 3 years. The antibody response to the rubella vaccine was significantly lower in the children with rAOM. The responses to tetanus and to diphtheria did not differ between children with and without rAOM. Thus, the results indicate that in addition to the known lack of antibodies against pneumococcal polysaccharide antigens, a lower antibody response against at least one protein antigen may exist in otitis-prone children.

KEY WORDS — acute purulent otitis media, antibodies, immune response, vaccination.

INTRODUCTION

More than two thirds of all preschool children at some time undergo at least one episode of acute purulent otitis media (AOM). About 10% of these children exhibit recurrent AOM (rAOM), in which pneumococci are the most commonly isolated microorganisms.[1,2] Immunologic mechanisms have been proposed to be critical factors in the development of rAOM. It is well known that the presence of hypogammaglobulinemia is a factor predisposing for bacterial infection; this fact may partly explain why AOM is generally confined to individuals with physiologic hypogammaglobulinemia, ie, to the age group 6 months to 2½ years. However, it does not explain why certain children are more heavily affected than others.

In comparisons of children with rAOM and non-otitis-prone children, certain immunologic discrepancies have been observed. Thus, children with rAOM exhibit aberrations within the complement system,[3,4] and lower serum concentrations of specific antibodies against AOM-associated pneumococci.[5,6] The lower levels of pneumococcal antibody concentrations in children with rAOM, as compared with non-otitis-prone children, were only manifest in the IgG and IgA classes, and the differences disappeared as the children grew up,[6,7] indicating a possible functional immaturity of otitis-prone children in their response to certain polysaccharide antigens.[6]

Otitis-prone children have also been reported to exhibit low serum concentrations of bactericidal antibodies against nontypeable *Hemophilus influenzae.*[8] Since antibodies against nontypeable *H influenzae* are generally directed against outer membrane proteins, this finding suggests that the immunologic response to some protein antigens may also be poor in these children. To further elucidate this possibility, we compared antibody responses to diphtheria, tetanus, and rubella vaccinations in children with rAOM and children with no history of AOM episodes.

MATERIALS AND METHODS

STUDY MATERIAL AND SAMPLES

Children born from November 1982 to February 1984 at the University Hospital in Lund, a city in southern Sweden with approximately 60,000 inhabitants, were enrolled in this prospective study at birth with the informed consent of their parents. The children were observed for 3 years, and in the event of an acute illness, a specialist with particular interest in the study was consulted either at the Department of Pediatrics or at the Department of Otorhinolaryngology. Epidemiologic data were obtained from questionnaires answered by the parents, from special forms filled in at visits to either of the two departments, from other medical records, from the records of the child welfare centers, and from repeated interviews with each family involved. Serum samples were obtained in the acute and convalescent phases of infection episodes, as well as regularly at birth and at the ages of 6 weeks and 3, 6, 12, 18, 24, 30, and 36 months.

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We diagnosed AOM by otomicroscopy and defined it as an acute episode of earache in a child with red bulging eardrum(s) or with purulent ear discharge, occasionally febrile and with signs of upper respiratory tract infection. (Relapse during antibiotic treatment or within 2 days of its completion was not counted as a new AOM episode.) Recurrent AOM was defined as six or more episodes of AOM during a 12-month period.

Of the 122 children originally enrolled in the study, 113 completed the follow-up. Of these 113 children, 13 developed rAOM — on average 11.2 AOM episodes per child during the observation period — and another 29 children experienced no AOM episode at all and had less than six acute respiratory tract infections diagnosed by a physician (healthy children). The sex distribution in these two groups was five girls and eight boys, and 14 girls and 15 boys, respectively (not significant by Fisher's exact test). Neither were any significant differences noted between these two groups of children regarding duration of breast-feeding, age at enrollment in either family day-care homes or in day-care centers, or total time spent in day-care outside the home.[9]

All the children were subject to the Swedish vaccination schedule, which by routine includes primary vaccination against diphtheria and tetanus, consisting of three doses of diphtheria/tetanus toxoid containing 12.5 flocculation units (Lf) diphtheria and 3.75 Lf tetanus toxoid per dose administered at intervals of 4 to 6 weeks, beginning at the second or third month of life. The routine schedule also includes immunization against rubella (together with measles and mumps), consisting of one single dose with live, attenuated virus at the age of 18 to 24 months. Vaccinations in uniform lots were given by nurses at the child welfare centers, where the records of immunization also were kept.

The antibody responses to diphtheria, tetanus, and rubella were analyzed both in rAOM children and healthy children. Preimmune sera (vis-à-vis diphtheria and tetanus) were obtained at 6 weeks of age. Postimmune analyses were generally performed in the sera obtained at either 6 or 12 months of age, depending on when the third dose had been given. The interval between this third dose and collection of postimmune serum samples was at least 1 week, and did not differ between the groups (median, 3 weeks for the rAOM children and 4 weeks for the healthy children). In seven children altogether, a comparison was made between the antibody titers in serum samples obtained at 1 to 2 weeks and at 3 to 6 months after the last vaccine dose.

For analysis of the antibody response against rubella, the preimmune sera were obtained at 18 months of age. The median interval between vaccination and collection of postimmune serum samples was 5 months for the rAOM children, as well as for the healthy control children (Table 1).

TABLE 1. HEMOLYTIC ZONE DIAMETER RELATED TO INTERVAL BETWEEN VACCINATION AGAINST RUBELLA AND COLLECTION OF POSTIMMUNE SERUM SAMPLE

*Interval** *(mo)*	*Hemolytic Zone (mm)†*	
	rAOM	*Healthy*
1	6	8, 11, 11
2	7, 8, 11, 11	8, 12
3		10, 11
4	9	10, 10, 10
5		9, 9, 10, 10, 11
6	10, 11	8, 10, 10, 10, 11, 13
7		11
8	8	11
9	7	11, 12
10		
11		10
12		
13		9
14		
15	6	
16		
17		9
18	10	

rAOM — recurrent acute purulent otitis media.

*Median interval was 5 months for rAOM children (mean, 6.25 months) as well as for healthy children (mean, 5.7 months) ($p = .897$).

†Median hemolytic zone was 8.5 mm for rAOM children (mean, 8.7 mm) and 10 mm for healthy children (mean, 10.2 mm) ($p = .027$).

DETERMINATION OF ANTIBODY CONCENTRATIONS

Diphtheria Antitoxin. Diphtheria antitoxin was measured with a micro-cell culture method using Vero cells.[10,11] The tests were carried out on microplates with 96 wells. The dilution step of the serum-neutralizing toxin in 50% of the cultures was taken as the titer. Titration was carried out with 25-μL dilution loops in fourfold steps from 1:8 up to 1:8,192. Twenty-five microliters of challenge toxin (100 tissue culture toxic doses) was added to each well. The plates were incubated for 60 minutes at 37°C before adding Vero cells (10^5 cells/mL) in 100 μL culture medium. Eagle's minimal essential medium enriched with 4% calf serum was used as the culture medium. The potency of the toxin in each test was determined by titration against the World Health Organization standard for diphtheria antitoxin.

The correlation between antitoxin titers determined with this micro-cell culture method and with the rabbit skin test[12] has earlier been shown to be good.[13] Values are given in international units per milliliter.

Tetanus Antitoxin. An enzyme-linked immunosorbent assay (ELISA) was performed in microtiter trays coated with tetanus toxoid at a 10^{-4} dilution in carbonate buffer (0.075 Lf/mL) overnight.[14] After washing with phosphate-buffered saline, serum in a twofold dilution series was added. On each plate a pooled serum with known antitoxin concentration (3 IU/mL) was titrated for comparison. The antitoxin concentration of this standard serum had been

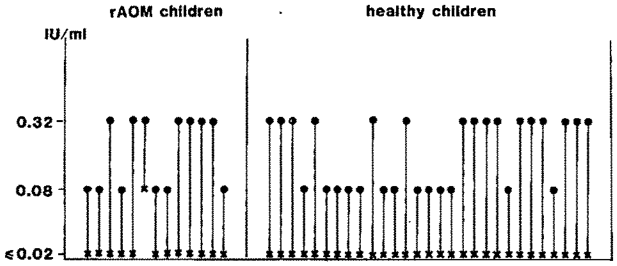

Fig 1. Diphtheria antitoxin titers before (x) and after (•) vaccination in 13 children with recurrent acute purulent otitis media (rAOM) and in 29 healthy children, as determined by ELISA.

determined relative to the international standard for tetanus antitoxin in potency assays in mice. After incubation, we added horseradish peroxidase-conjugated rabbit anti human immunoglobulin (Dakopatts, Denmark). The antitoxin concentration in each serum sample was calculated relative to that of the standard, assuming a linear relationship between the log serum concentration in a well and the log of absorbance obtained from that well. Values are given in international units per milliliter.

A good correlation has earlier been demonstrated[15] between the antibody values obtained with this ELISA method and those obtained with the toxin neutralization test in mice.[16]

Antibodies Against Rubella Virus. These were quantified with a single radial hemolysis (hemolysis-in-gel) test, performed essentially as described by Strannegård et al.[17] Test results were assessed blindly (ie, the investigator was unaware whether serum samples belonged to otitis-prone or healthy children). In brief, rubella hemagglutination antigen (Orion), diluted 1:20, was incubated with pigeon erythrocytes. After centrifugation, the erythrocytes were resuspended and mixed with agarose (type L, Behringwerke; final concentration, 0.7%), the suspension being poured into rectangular plastic forms (Integrid, Becton-Dickinson). After solidification, 3-mm diameter holes were punched out and filled with inactivated, undiluted serum. The plates were incubated for 24 hours at 4°C, and then normal guinea pig serum, diluted 1:2, was poured on top of the gel. After incubation for 15 minutes at room temperature and 2 hours at 37°C, hemolytic zones were measured manually.[17] To exclude unspecific hemolysis, sera were simultaneously tested in a corresponding gel without rubella antigen. The values are given as millimeters of hemolytic zone.

Because of the lack of some sera, only 12 of 13 rAOM children and 28 of 29 healthy children could be investigated for antibody response to rubella.

STATISTICAL METHODS

The χ^2 test and the Mann-Whitney *U* test were used for statistical analysis.

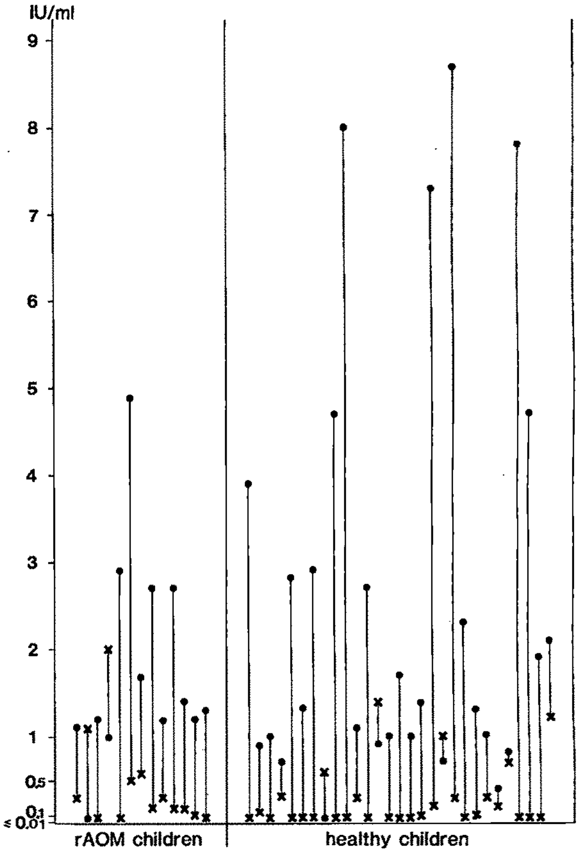

Fig 2. Tetanus antitoxin concentrations before (x) and after (•) vaccination in 13 children with recurrent acute purulent otitis media (rAOM) and in 29 healthy children, as determined by ELISA.

RESULTS

The preimmunization concentration of antibodies against diphtheria toxoid was ≤0.02 IU/mL in all but one of the children (Fig 1). After immunization, the antibody concentration reached 0.08 IU/mL in 6 of 13 (46%) of the rAOM children and in 13 of 29 (45%) of the healthy control children, and 0.32 IU/mL in the remaining children (Fig 1). No differences were noted between rAOM and healthy children.

The serum concentrations of antibodies against tetanus toxoid are shown in Fig 2. Twelve of 29 (41%) healthy children and 10 of 13 (77%) rAOM children had preimmunization antibody concentrations of ≥0.1 IU/mL (not significant). All postimmune antibody concentrations were ≥ 0.01 IU/mL (five children had lower values after immunization than before) (Fig 2). Although antibody responses tended to be higher in the healthy children (mean, 2.34 IU/mL) than in the rAOM children (mean, 1.38 IU/mL), the difference was not significant (Fig 2).

In seven children studied, concentrations of antibodies against diphtheria and tetanus were of about the same magnitude in the paired serum samples obtained at 1 to 2 weeks and 3 to 6 months after im-

TABLE 2. CONCENTRATIONS OF ANTIBODIES AGAINST TETANUS AND DIPHTHERIA MEASURED IN PAIRED SERUM SAMPLES OBTAINED AT 1 TO 2 WEEKS AND 3 TO 6 MONTHS AFTER IMMUNIZATION

	*Tetanus (IU/mL)**		*Diphtheria (IU/mL)**	
Children	*1-2 wk*	*3-6 mo*	*1-2 wk*	*3-6 mo*
Healthy				
1	8.0	2.4	0.32†	0.08†
2	0.9	1.8	0.32	0.08
3	8.7	5.3	0.32	0.32
4	0.3	0.4	0.32	0.32
5	1.9	0.8	0.32	0.08
rAOM				
6	1.4	1.0	0.32	0.32
7	1.2	1.7	0.32	0.32

rAOM — recurrent acute purulent otitis media.

*See Materials and Methods.

†Difference between 0.08 and 0.32 represents one step of titration.

munization (Table 2).

In the preimmune sera, none of the children had any demonstrable antibodies against rubella virus. In the postimmune sera the healthy children exhibited significantly higher antibody concentrations than did the rAOM children ($p = .027$), the mean hemolytic zones being 10.2 mm (range, 8 to 13) and 8.7 mm (range, 6 to 11), respectively (Fig 3). The diameters of the hemolytic zones were of the same magnitude irrespective of whether the postimmune sera were obtained early or late after the vaccination (Table 1).

DISCUSSION

When the serum concentrations of the total immunoglobulins of the classes IgG, IgA, and IgM were analyzed, they were not found to be lower in otitis-prone children than in non–otitis-prone children.[18,19] The serum concentrations of specific antibodies against certain pneumococcal types were, on the other hand, found to be lower in otitis-prone children.[5-8] This divergence has been proposed to depend on a selective inability of otitis-prone children to respond adequately to certain polysaccharide antigens, a suggestion deriving support from recent findings by Pelton et al,[20] who reported poorer antibody response to pneumococcal vaccine in otitis-prone children than in non–otitis-prone children.

One explanation proposed to account for the poor antibody responses against AOM-associated microorganisms seen in children with frequent AOM episodes is delayed immunologic maturation in children with rAOM.[7] Support for this hypothesis has been provided by studies of blood lymphocyte subpopulations. As compared with age-matched non–otitis-prone children, otitis-prone children exhibited higher frequencies of blood lymphocytes expressing B-cell surface antigens indicating immaturity (CD19, CD24, CD20, CD22).[21] Whether this is related to the otitis-prone children's poor ability to produce certain specific antibodies is not known, however.

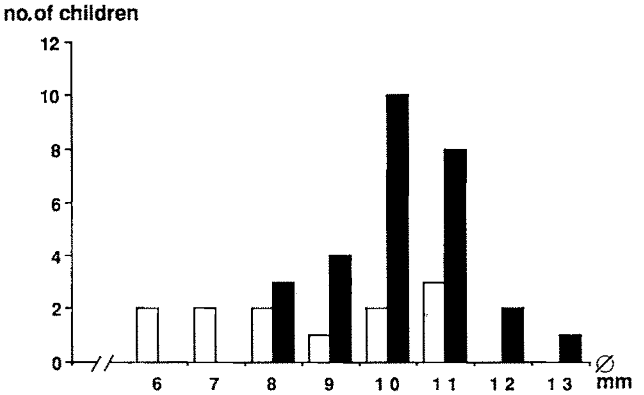

Fig 3. Serum antibody response to rubella vaccination in 12 children with recurrent acute purulent otitis media (light bars) and in 28 healthy children (dark bars) as determined with hemolysis-in-gel test. Values represent diameter (mm) of hemolytic zone. Groups differ significantly ($p = .027$). All preimmunization values were nil.

The poor antibody response to the rubella vaccine seen in the present study in the rAOM children, when compared with non–otitis-prone children, is in contrast to the responses to diphtheria and tetanus vaccination, which did not differ significantly between the two groups. These results do not mean that otitis-prone children are more prone to rubella infection than healthy children, but they are in agreement with the just-discussed inability regarding some selective antibody responses in the rAOM children — but with the important addition that the antibody responses might be lower in the rAOM children not only when stimulated with some pneumococcal polysaccharide antigens, but also with at least one antigen with protein characteristics. This finding suggests the possibility of a more comprehensive immunologic divergence in otitis-prone children than has earlier been discussed. Although rubella, tetanus, and diphtheria are not known to be associated with AOM, they were chosen for study 1) because of the protein characteristics of the antigens[22,23] (as a complement to previous investigations on pneumococcal polysaccharide antigens), 2) because the methods available for antibody detection required only small quantities of sera, and 3) because almost all Swedish children are routinely immunized against these agents.

Vaccination with currently available pneumococcal vaccines has so far been unsuccessful in preventing AOM in small children.[24-26] The poor antibody responses have been ascribed to a lack of immunogenicity of some polysaccharide antigens in infants and young children.[27,28] In accordance with this view, it has been proposed that the pneumococcal vaccines be modified to render them capable of provoking an antibody response similar to that obtained with protein antigens.[29] According to present opinion regarding the poor response to rubella vaccine, however, the chances of succeeding in this are not uniformly encouraging.

The absolute concentrations of antibodies to diphtheria and tetanus found in the present study are in accord with the results of previous studies of antibody concentrations after tetanus/diphtheria vaccination in children, all of whom responded with serum concentrations of tetanus antitoxin regarded as protective, but several of whom responded with inadequate concentrations of diphtheria antitoxin.[13,15]

The results of the present study indicate that in addition to the known selective lack of antibodies against some AOM-associated pneumococcal types, a lower amount of antibodies also against other antigens may exist in otitis-prone children. In this context, the observation that children with rAOM also seem to contract other respiratory tract infections more frequently than do non–otitis-prone children is of interest.[9,30]

ACKNOWLEDGMENTS — We are indebted to our colleagues Olof Kalm and Ragnhild Kornfält for their invaluable contributions.

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NASOPHARYNGEAL CRANIOPHARYNGIOMA

CASE REPORT AND LITERATURE REVIEW

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Craniopharyngioma is an intracranial tumor that occurs rarely in the infrasellar region. Eight patients with craniopharyngioma located within the nasopharynx have been reported previously. These cases originated in the nasopharynx and involved the sella turcica (6), the sphenoid sinus (1), and the vomer (1). Craniopharyngioma usually originates intracranially. When there is no evidence of sellar involvement, the tumor most likely arises along the path of the craniopharyngeal duct. According to the neurosurgical literature, the optimal treatment consists of total surgical excision. Incomplete tumor removal is supplemented by adjunctive radiotherapy, which has been shown to significantly increase the survival rate. A patient with craniopharyngioma of the nasopharynx and paranasal sinuses who presented with nasal obstruction is reported. Radiographic studies were employed for tumor evaluation, and biopsy was done to establish the histopathologic diagnosis. Treatment included a combination of surgical excision and irradiation.

KEY WORDS — craniopharyngioma, nasopharynx.

INTRODUCTION

Craniopharyngioma is a benign epithelial neoplasm primarily confined within the boundaries of the skull. It comprises approximately 3% of all intracranial tumors. The tumor arises in the area of the sella turcica, with a suprasellar location being the most common. Rare lesions have been described within the sella, the third ventricle, and the infrasellar region. The infrasellar tumors can be located within the sphenoid bone and nasopharynx, and thus extend beyond the boundaries of the skull.[1-3]

Embryology. There are several theories regarding the origin of craniopharyngioma. Most of them are based on the embryologic development of the adenohypophysis. The tumor is postulated to arise from the remnants of the pharyngeal hypophysis. In the fourth week of gestation, an ectodermally lined diverticulum develops in the roof of the stomodeum just anterior to the oropharyngeal membrane. This is the pouch of Rathke, and it ascends cranially to meet the neuroectoderm of the infundibulum (neurohypophysis), which descends as a neural outgrowth from the floor of the third ventricle (diencephalon) of the embryonic brain. Rathke's pouch eventually differentiates into the anterior lobe of the pituitary, the adenohypophysis. The path traversed by Rathke's pouch remains as a solid cord of cells connecting the rudimentary adenohypophysis to the ectoderm of the stomodeum. Later in the embryonic life this cord disintegrates, leaving an obliterated craniopharyngeal canal. It is a tract that runs from the anterior part of the hypophyseal fossa of the sphenoid bone to the exterior of the skull, to the junction of the posterior septum of the nose with the palate, which is the stomodeal end of the recess.[4]

Theory of Origin. The theory of the origin of craniopharyngioma along the tract of the obliterated craniopharyngeal duct was first proposed in 1904 by Erdheim,[5] who observed the pharyngeal hypophysis to be located on the posterior edge of the vomerine bone. In 1931 Carmichael[6] found remnants of the obliterated craniopharyngeal duct in the immediate region of the pituitary gland in 32.7% of the autopsy cases he studied. McGrath[7,8] later demonstrated the presence of functioning pharyngeal hypophysis in the adult, with a vascular communication from the hypothalamic-hypophyseal portal system through the sphenoid bone to the vascular bed of the pharyngeal hypophysis. Craniopharyngioma may originate anywhere along the tract of the obliterated craniopharyngeal duct, and further, within the functioning pharyngeal hypophysis itself. This could account for an infrasellar location of the tumor along the posterior aspect of the vomer above the junction of the soft palate and nasal septum, the sphenoid bone, and the undersurface of the floor of the sella.

Clinical Presentation. Craniopharyngiomas can arise at any age, although most occur in the first two decades of life.[1] Symptoms and clinical findings are related to the tumor's mass effect and compression of the surrounding structures. The optic chiasm is commonly affected, often with visual changes such as blurred vision, diplopia, visual field defects (mostly bitemporal hemianopsia), bizarre scotomata patterns, and blindness. Headache is a frequent symptom, and may be accompanied by vomiting. Other findings include hydrocephalus and papilledema, as well as hypopituitarism secondary to anterior pituitary dysfunction. Mental changes and occasional cranial nerve involvement are also observed.[3,9]

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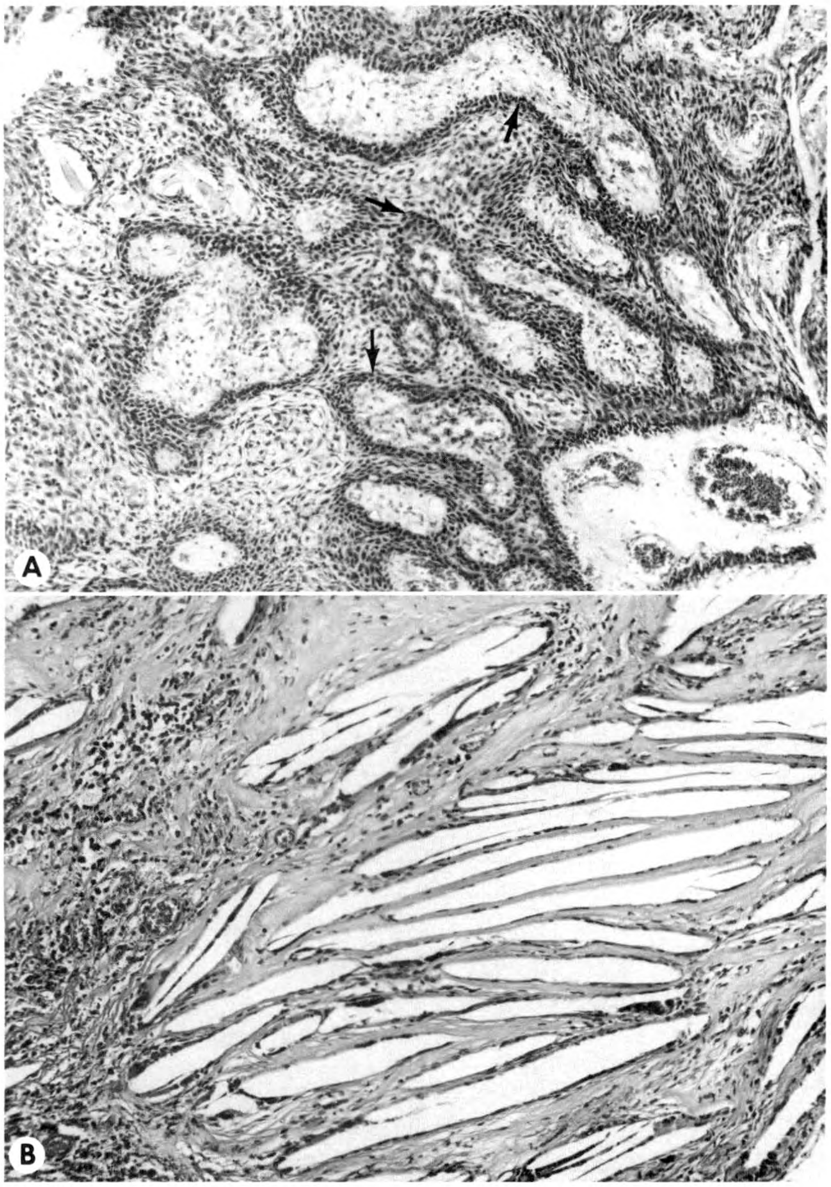

Fig 1. Adamantinomatous craniopharyngioma demonstrating A) palisading rims of cuboidal or columnar epithelial cells arranged in characteristic pattern of cords, nests, and trabeculae (arrows) and B) degenerative changes with cholesterol clefts.

Diagnostic Evaluation. In evaluation of these tumors, radiographic studies are most helpful. Plain skull x-rays commonly show a suprasellar lesion with shortening and flattening of the dorsum sellae. Expansion and erosion of the sella turcica can be found with an intrasellar tumor. Multiple calcifications within the tumor are observed, especially in younger patients. In adults, craniopharyngiomas are often not calcified. Computed tomography usually reveals the heterogeneous nature of the tumor with its solid and cystic components. The extent of the soft tissue mass is well defined. Contrast studies or pneumoencephalography can be used to evaluate the hydrocephalus. Angiography is nonspecific for craniopharyngioma, reflecting only the presence of a mass.[10-12]

Other diagnostic studies include cerebrospinal fluid analysis for protein content. In tumors confined to the sella turcica, the protein content is normal. When extrasellar extension is present, there is usually an increase in protein.[13] Finally, the function of the anterior pituitary is evaluated to assess the extent of the gland involvement.

Pathology. On a gross pathologic evaluation, craniopharyngioma is found to be of variable size, and cystic more often than solid. The cysts contain a yellow to dark fluid, laden with glistening cholesterol crystals, resembling "motor oil." The tumor is usually adherent, with invasion into the surrounding structures that prevents a complete removal. Microscopically, the tumor is subclassified into two types: adamantinomatous craniopharyngioma and papillary craniopharyngioma (suprasellar papillary squamous epithelioma). The adamantinomatous craniopharyngioma is usually nodular and multicystic. It consists of solid areas in which epithelial cells assume the adamantinomatous pattern with variable architecture of anastomosing trabeculae, nests,

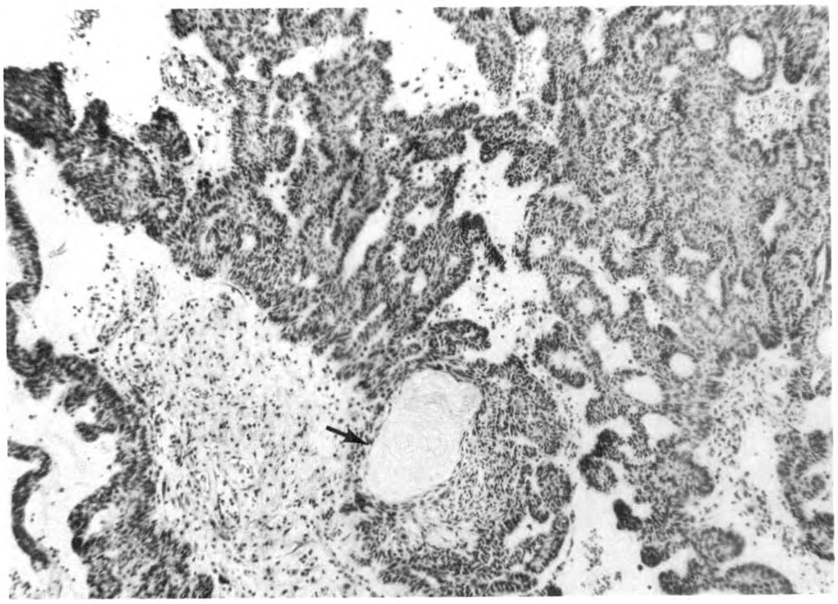

Fig 2. Papillary squamous craniopharyngioma consisting of well-differentiated squamous epithelial cells arranged as papillae lined with loose connective tissue. Note presence of keratin pearl (arrow).

cords, and cysts (Fig 1A). These are surrounded by a characteristic pattern of a palisading rim of cuboidal or columnar epithelial cells resting on a basement membrane. Interspersed among them are areas of compact epithelial whorls and nodular foci of keratinization. Cyst formations are characterized by degenerative changes with cellular necrosis, calcifications, and cholesterol clefts (Fig 1B). The second type, squamous papillary craniopharyngioma, consists of cords and papillae of squamous epithelium separated by loose connective tissue stroma (Fig 2). Calcifications, palisaded cells, and keratoid nodules are rare. This type occurs predominantly in adults. Craniopharyngioma is a benign tumor, and to date no histologic malignancies have been reported.[1,2]

Treatment. Treatment of these tumors is mostly excisional, through a craniotomy or transsphenoid approach.[14] Earlier methods involved aspiration of a single cyst, evacuation of a multicystic mass, or tumor marsupialization. This relieved the pressure of the growing cyst, and thus led to a symptomatic improvement. Frequently, the cyst would recur, with return of symptoms. Complete removal of the tumor is the preferred procedure. This is often technically difficult because of adherence to surrounding structures. Residual epithelium that is left behind can be the source of recurrence.

Various adjunctive treatments have been tried to

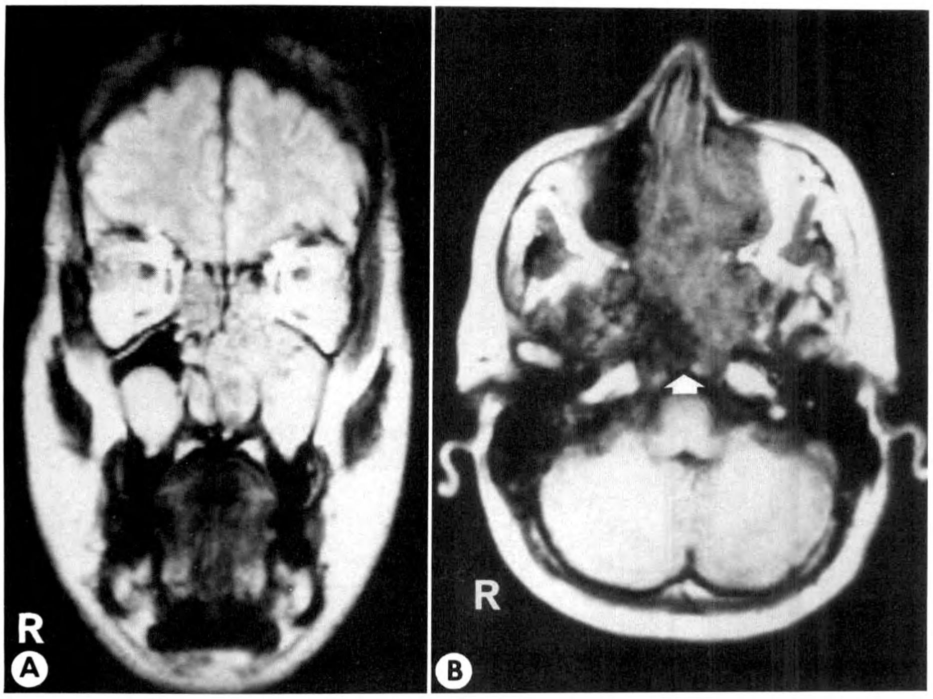

Fig 3. Nuclear magnetic resonance scans. A) Coronal view demonstrating soft tissue mass filling left nasal fossa, left maxillary sinus, and bilateral ethmoid air cells. Mass has nonhomogeneous density, with areas of very low signal intensity consistent with calcifications. High signal intensity in right maxillary sinus indicates mucous retention cyst. B) Axial view showing tumor mass present within nasal fossa, right maxillary sinus, and nasopharynx. Lesion extends into bony clivus (arrow).

NASOPHARYNGEAL CRANIOPHARYNGIOMA CASE REPORTS

Author	*Year*	*Patient* *Age*	*Patient* *Sex*	*Symptoms*	*Physical Findings*
Drummond[24]	1938	14	F	Nasal obstruction, headache, loss of vision (L), decreased vision (R)	NPX and bilateral NF mass, hard and soft palate flattening, blindness (L), decreased vision (R)
Podoshin et al[25]	1970	15	F	Nasal obstruction, chronic sinusitis	NPX and bilateral NF mass
Prasad and Kwi[26]	1975	55	F	Nasal obstruction	NPX and bilateral NF mass
		48	M	Nasal obstruction, headache, diplopia, face hypoesthesia (L)	NPX and (L) NF mass, lateral rectus weakness (L), infraorbital nerve hypoesthesia (L)
Illum et al[27]	1977	14	F	Headache, decreased vision (L), diplopia	Abducens nerve palsy (L), temporal hemianopsia (L)
Majlessi et al[28]	1978	17	M	Headache, blurred vision, mental status changes	NPX mass, hard palate erosion, bitemporal hemianopsia, exophthalmos, hypertelorism, hypopituitarism
Lewin et al[29]	1984	27	F	Epistaxis	NPX pedunculated mass
Maier[30]	1985	77	M	Headache, fluid drainage from NPX	NPX drainage of fluid, CSF rhinorrhea
This report	1990	29	M	Nasal obstruction	NPX and bilateral NF mass

NPX — nasopharynx, NF — nasal fossa, CSF — cerebrospinal fluid.

prevent recurrence. They include instillation of radioactive agents such as gold, phosphorus, or yttrium into the tumor bed, intracystic chemotherapy, and systemic chemotherapy.[15,16]

Radiotherapy, once considered ineffective, is currently the adjunctive treatment most often used. Craniopharyngioma has been found to be radiosensitive, and radiotherapy plays a major role in preventing recurrence and improving survival.[17] Study of autopsy cases by Kramer[18] showed total destruction of residual tumor cells by radiotherapy. Amacher[19] reported that in a patient who had a subtotal tumor removal followed by radiotherapy, the remaining craniopharyngioma was completely necrosed.

In the neurosurgical literature, the advocated treatment of intracranial craniopharyngioma is total removal of the tumor, which is possible in selected cases. Amacher[19] stated that total excision of a tumor offers the best chance of long-term survival. When vital structures are involved and excision is compromised by significant risks of morbidity and mortality, subtotal removal of the tumor followed by supplemental radiotherapy is the preferred treatment. Postoperative radiotherapy has been reported by many authors to increase the recurrence-free survival rates.[19-21] In a recent study by Manaka et al[17] the 5- and 10-year survival rates were 88.9% and 76.0% for the irradiated group, and 34.9% and 27.1% for the control group (nonirradiated), respectively. The study revealed a high statistical significance in the difference between the survival times of the irradiated and control groups ($p < .0001$). Cavazzuti et al[22] and Danoff et al[23] investigated radiotherapy's effects on the brain, and they concluded that the effects of irradiation are comparable to those of surgical excision alone. Thus, the recommended treatment for craniopharyngioma is surgical excision, followed by radiotherapy in patients in whom total excision is not successful.[17-20] Since the long-term effects of irradiation on the brain tissue are not well known, long-term follow-up of the patients is necessary.[21]

CASE REPORT

A 29-year-old man presented with a complete left nasal airway obstruction that had developed over a period of 3 years. One month prior to admission, a partial right nasal obstruction was noted. Examination revealed a mass in the left nasal fossa 1 cm from the vestibule, completely obstructing the airway. The right nasal fossa had a deviated septum with a mass present at the choana. The nasopharynx was totally occupied by a tumor. The remainder of the examination findings were normal. Results of routine laboratory tests were unremarkable.

Sinus x-ray films revealed opacification of the left maxillary, posterior ethmoid, and sphenoid sinuses. There was destruction of the bony septa of the posterior ethmoid air cells and thinning of the medial wall of the left maxillary sinus. A mucous retention cyst was present in the right maxillary sinus. Computed tomography showed a large soft tissue mass occupying the left nasal fossa, the nasopharynx, and the left sphenoid sinus.

Magnetic resonance imaging showed a large expansile mass within the left nasal fossa, the left maxillary sinus, the nasopharynx, and the left sphenoid sinus (Fig 3A). The mass extended posteriorly into the bony clivus (Fig 3B). It was nonhomoge-

NASOPHARYNGEAL CRANIOPHARYNGIOMA CASE REPORTS (Continued)

Radiographic Findings	*Treatment*	*Tumor Location*	*Follow-up*
SXR: ST floor flattening, SS expansion and erosion	Transnasal tumor debulking	ST, SS, NPX	Not reported
SXR: ST enlargement, SS erosion, hard palate erosion, tumor calcifications	Transpalatal tumor debulking	ST, SS, NPX	Not reported
SXR, TG: ST floor erosion, SS erosion, NPX mass; AG: avascular mass	Transpalatal tumor debulking	SS, NPX	Not reported
SXR, TG: ST expansion and erosion	NPX biopsy with tumor drainage (surgical excision refused)	ST, SS, NPX	Not reported
TG: ST and SS erosion, NPX mass; AG: avascular mass	Craniotomy, biopsy, irradiation (54 Gy), transpalatal tumor debulking	ST, SS, NPX	Not reported
SXR: ST expansion and erosion, tumor calcifications	Craniotomy, biopsy	ST, SS, NPX	Not reported
SXR, TG: no lesion; CT: NPX mass; AG: normal	Transpalatal en bloc tumor removal	NPX	Not reported
SXR, TG: ST destruction, SS and NPX mass, petrous bone erosion (L), tumor calcifications	Radiotherapy (24 Gy, 41 Gy)	ST, SS, NPX	Alive 8 yr after second course of radiotherapy
SXR, CT: SS, NPX, ES, and MS mass; MRI: multicystic mass	Lateral rhinotomy approach for tumor, radiotherapy (54 Gy)	SS, ES, MS, NPX	No recurrence after 36 mo

SXR — skull x-ray, ST — sella turcica, SS — sphenoid sinus, TG — tomogram, AG — angiogram, NPX — nasopharynx, CT — computed tomography, ES — ethmoid sinuses, MS — maxillary sinus, MRI — magnetic resonance imaging.

neous in consistency, with a suggestion of multiple tiny cysts and calcifications. The right maxillary sinus had a signal intensity consistent with a mucous retention cyst. The sella turcica, suprasellar region, brain parenchyma, and cerebrospinal fluid spaces were entirely normal. Carotid and vertebral angiography revealed that the tumor was avascular and that there was no evidence of intracranial invasion. Results of a biopsy of the left nasal mass were consistent with craniopharyngioma.

The decision was made to treat the tumor with surgical excision followed by postoperative radiotherapy. A lateral rhinotomy approach was selected to obtain the best exposure of the left nasal fossa, the nasopharynx, and the left paranasal sinuses. A Weber-Fergusson lip-splitting incision was used and carried down through the periosteum laterally. Lateral and medial osteotomies were performed, and the nasal bones were reflected to the right. The left nasal fossa was visualized, and the tumor was exposed. An intraoperative frozen section confirmed the diagnosis of craniopharyngioma. The maxillary sinus was entered, and the anterior antral wall was removed with a drill. The tumor had destroyed much of the medial wall of the maxillary sinus and the lateral wall of the nasal fossa. The anterior ethmoid air cells were exposed next. The tumor involved the left nasal fossa, the left maxillary sinus, the left anterior and posterior ethmoid sinuses, and the entire nasopharynx. The tumor was intimately attached to the anterior wall of the sphenoid sinus and the clivus, but not to the nasal fossa, maxillary sinus, or ethmoid sinuses. The tumor was removed in several large pieces with minimal bleeding. The ethmoid sinuses were curetted. The anterior wall of the sphenoid sinus was removed, and tumor was found to infiltrate the posterior wall of the sinus, as well as the clivus. With use of the operating microscope the outer cortex of these bones was drilled to expose the bone marrow. It was elected to leave the posterior cortex with gross tumor within the crevices of the marrow of the clivus and the posterior wall of the sphenoid sinus. The left nasolacrimal duct was cannulated. Posterior and anterior nasal packs were inserted for hemostasis, and the wound was closed meticulously.

On gross inspection, the tumor consisted of solid areas, as well as cystic spaces filled with dark brown, oily fluid. Histopathologic evaluation of the tumor revealed multiple cysts and an adamantinomatous pattern, consistent with craniopharyngioma, of anastomosing cords lined by stellate epithelial cells with a single layer of peripheral palisading cells. There was squamous metaplasia with keratin production and focal calcifications.

The patient underwent an uneventful recovery. On the fourth postoperative day, the posterior nasal pack was removed. This was done in the operating room with general anesthesia. The patient was discharged from the hospital on the eighth postoperative day. Radiotherapy consisting of a total of 54 Gy (30 fractions) was administered 1 month later. The nasolacrimal duct cannula was removed after completion of radiotherapy. The lacrimal system remained patent, without evidence of epiphora. The patient is free of disease 3 years later.

LITERATURE REVIEW

In the literature, eight cases of extracranial craniopharyngioma have been described, all occupying the nasopharynx (see Table[24-30]). In six patients, this tumor involved the nasopharynx, as well as the sella turcica and the sphenoid sinus. One patient had the tumor within the nasopharynx and the sphenoid sinus only. Another patient had craniopharyngioma solely confined to the nasopharynx. In our patient, the tumor occupied the nasopharynx and the left sphenoid sinus, as well as the left ethmoid and maxillary sinuses.

Nasal obstruction was observed in five patients, and epistaxis occurred in one. Physical examination revealed nasopharyngeal and/or nasal fossa masses in eight patients. In six cases with sella turcica involvement, headache, visual changes, and other central nervous system findings were noted.

Skull x-ray study, tomograms, and computed tomography were the most common radiographic techniques employed in evaluation. They showed tumor expansion, bony erosion, and calcifications in a majority of the patients. In addition, our patient had magnetic resonance imaging, which detected a multicystic nature of the tumor, a presence of calcifications, and no evidence of sella turcica involvement. Angiography was done in four cases, confirming tumor avascularity.

The Table further displays that surgical excision and radiotherapy were the main modes of treatment. A transnasal approach was used in the earliest reported case (1938).[24] In four patients, a transpalatal removal was performed. Biopsy only was done in two patients, one via craniotomy, and the other of the nasopharynx. Our patient underwent tumor removal through a lateral rhinotomy approach. Radiotherapy was the only mode of treatment in one patient, and in another it was performed prior to operation. Our patient had postoperative radiotherapy.

Information on long-term patient follow-up is unavailable. Six patients who underwent tumor excision had initial resolution of symptoms. In two patients, one with biopsy only and another who was treated with radiotherapy, a progression of the disease was observed. Our patient remains free of disease 3 years after treatment.

DISCUSSION

Craniopharyngioma is a rare tumor. It arises within the sella turcica and expands mainly into the suprasellar region. Occasionally, the tumor can occur without sellar involvement. This infrasellar craniopharyngioma may then originate anywhere along the tract of the obliterated craniopharyngeal duct, which would include the sphenoid bone, vomer, and nasopharynx; thus, Erdheim's theory[5] is supported.

Surgical excision is the treatment of choice. The transpalatal approach for the infrasellar and intrasellar tumors has been the advocated technique. This surgical procedure was first recommended in 1927 by Loeb.[31] It was later popularized by Owens[32] and Wilson.[33] Johnson[9] described a case of craniopharyngioma of the intrasellar region with involvement of the sphenoid sinus, and was the first to apply the transpalatal approach for the tumor's removal. Subsequently, other surgeons (Podoshin et al,[25] Prasad et al,[26] Illum et al,[27] and Lewin et al[29]) adopted Johnson's approach in cases of craniopharyngioma within the nasopharynx. The transpalatal approach, although it gives a good exposure of the nasopharynx and the posterior nasal cavity, can be too restrictive in extensive tumors. In addition, a significant velopalatine insufficiency can result. The lateral rhinotomy approach, first described in 1845 by Fergusson,[34] provides adequate exposure of tumors occupying the nasopharynx, nose, and paranasal sinuses. By using this approach we had a complete visualization of the tumor, and we were able to remove it all except the part infiltrating the clinoid bone marrow. The ability to have direct vision while working near the vital structures reduced the risks of potential intraoperative complications. We recommend this approach for the best visualization of infrasellar craniopharyngioma.

When complete removal of the tumor is not possible, postoperative radiotherapy is the advocated treatment in patients with intracranial craniopharyngioma. We propose a similar approach to nasopharyngeal craniopharyngioma. Combined surgical excision and postoperative radiotherapy has been shown to increase the survival rates. Long-term follow-up of patients is required.

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MELANOSIS OF THE LARYNX

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A case of laryngeal melanosis is presented. This is followed by the analysis of the total of nine cases reported in the English literature. Patients are men in their sixth to eighth decade of life who present with hoarseness. Histopathologic findings include pigment deposits in the basal layer of the laryngeal epithelium. The possible relation of this lesion to carcinoma of the larynx is discussed.

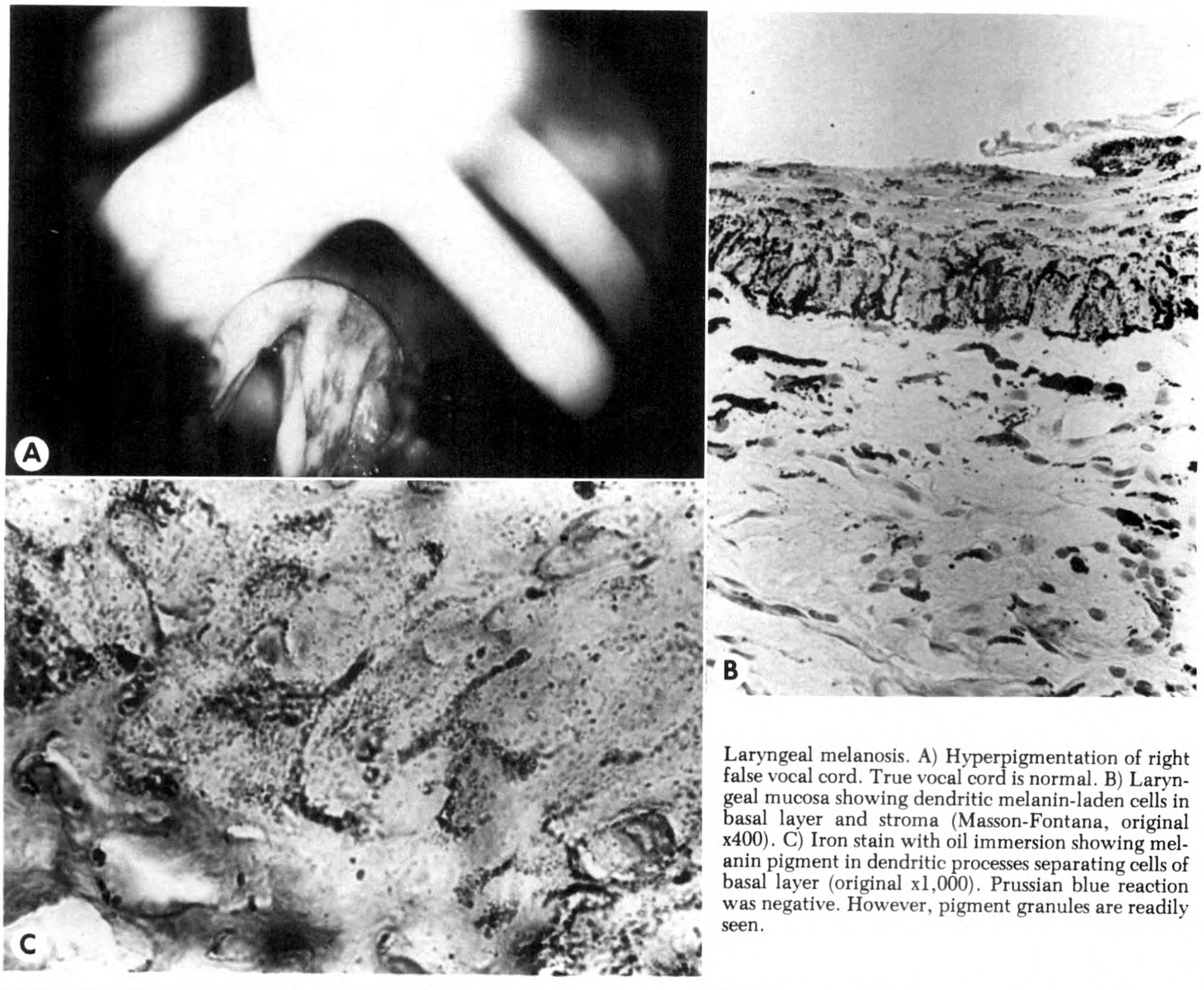
KEY WORDS — larynx, melanin, melanosis, premalignancy.

CASE HISTORY

A 58-year-old man presented with hoarseness of 18 months' duration. He had no other head and neck complaints. The patient had smoked two packs of cigarettes a day for 40 years. Laryngoscopy revealed diffused, patchy, linear, slightly raised, dark discoloration of both false vocal cords and the medial aspect of both aryepiglottic folds (see Figure, A). The vocal cords were normal. Multiple biopsy samples were taken.

PATHOLOGIC FINDINGS

Sections from the false vocal cords revealed acanthotic laryngeal epithelium overlying edematous



Laryngeal melanosis. A) Hyperpigmentation of right false vocal cord. True vocal cord is normal. B) Laryngeal mucosa showing dendritic melanin-laden cells in basal layer and stroma (Masson-Fontana, original x400). C) Iron stain with oil immersion showing melanin pigment in dendritic processes separating cells of basal layer (original x1,000). Prussian blue reaction was negative. However, pigment granules are readily seen.

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LARYNGEAL MELANOSIS

Author	*Sex*	*Age (yr)*	*Symptoms*	*Smoking*	*Laryngoscopy*	*Location*	*Melanin*	*Masson-Fontana Silver Technique*	*Associated Disorders*
DiGregorio and DeGaetani[8]	M	71	Hoarseness	NM	Slightly brown mucosa	Supraglottis	Basal layer, lamina propria	+	Squamous cell carcinoma
Pesce and Toncini[7]	M	60	Hoarseness	NM	NM	NM	Basal layer, stroma	+	Squamous cell carcima, chronic inflammation
	M	57	Hoarseness	NM	NM	Vocal cord	Basal layer, stroma	+	Acanthosis, parakeratosis
	M	53	Hoarseness	NM	NM	Vocal cord	Basal layer	+	Squamous metaplasia
	M	56	Hoarseness	NM	NM	Vocal cords	Basal layer	+	Parakeratosis
	M	73	NM	NM	NM	Vocal cord	Basal layer	+	Chronic inflammation
Busuttil[9]	M	65	Huskiness	NM, but coal miner with known pneumoconiosis	Chronic laryngitis	Vocal cords, anterior commissure	Basal layer	+	Acanthosis, chronic inflammation
Goldman et al[1]	NM	NM	(Laryngectomy)	NM	NM	Posterior supraglottis	Basal layer, mucous glands	+	Squamous cell carcinoma, status post radiotherapy
Present case	M	58	Hoarseness	+	Patchy discoloration	Supraglottis	Basal layer	+	Hyperkeratosis

NM — not mentioned in original article.

stroma. There was a conspicuous absence of inflammatory reaction. Easily recognized pigmented cells were present in the basal layer on the hematoxylin and eosin–stained sections, which also stained positively for melanin with Masson-Fontana stain (see Figure; B,C).

DISCUSSION

Melanocytes, which are ectodermal cells, originate in the neural crest. After the eighth week of gestation, they migrate to their ectodermal sites. Melanocytes are also present in the retina. The presence of melanocytes in the human larynx was documented by Goldman et al[1] in 1972. The origin of these cells, or melanocytes in any other nonintegumentary or extraocular sites, has been a subject of speculation. Theories attempting to explain the histogenesis include the transformation of epithelial cells to melanoblasts ("melanogenic metaplasia"), as proposed by Shivas and MacLennan[2]; the transformation of neural tissue into melanin-producing cells[3]; and the migration of melanoblasts with the mesoderm to different organs with subsequent maturation and melanin production.[4] Other interesting theories were related to the occurrence of melanomas in tissues that were not known to contain melanocytes, such as the lower respiratory tract. The possibility that these melanomas are metastatic lesions from occult primary tumors that had undergone spontaneous regression has been suggested by Campbell et al.[5] Reid and Mehta[6] mentioned the possibility of differentiation of squamous carcinoma cells into melanin-producing cells. This theory is especially interesting, because 37.5% of the cases of laryngeal melanosis reported in the literature were associated with squamous cell cancer.

Benign melanosis of the larynx is extremely rare. Extensive review of the English literature revealed eight cases.[1,7-9] Although the number is small, it seems that there are many similarities in the clinical and pathologic characteristics of these cases (see Table[1,7-9]). Patients are men in their sixth to eighth decade of life, who present with hoarseness. Laryngoscopy shows laryngitis with or without discoloration. Any region of the larynx may be affected. Histopathologic examination reveals pigmentation of the basal layer, which is stained positively by the Masson-Fontana silver technique.

Is laryngeal melanosis premalignant? The fact that 33.3% (three of nine) of the cases were associated with carcinoma, and 44.4% (four of nine) with parakeratosis, hyperkeratosis, or acanthosis, may indicate that there is some relation between these histologic conditions. However, to conclude that melanosis is precancerous would be premature. The reason is that there is no denominator for these ratios. We have no idea how many people in the general population have laryngeal melanosis and what percentage of them will develop malignant or premalignant lesions. As long as indirect laryngoscopy is not included in the general physical examination of people without voice complaints, we will not have the answer. Only prospective, longitudinal study will help us reach a conclusion. As an example, it is possible that both melanosis and carcinoma are related to a third factor, such as smoking, and melanosis itself may therefore not be a premalignant lesion.

ACKNOWLEDGMENTS — The authors thank Cornelius Mead and the Brooklyn Veterans Administration Medical Media Service for their assistance. We also thank Judith Reis for her assistance in preparing the manuscript.

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CERVICAL NECROTIZING FASCIITIS: AN UNCOMMON SEQUELA TO DENTAL INFECTION

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Necrotizing fasciitis is a soft-tissue infection, usually polymicrobial, that causes necrosis of fascia and subcutaneous tissue while sparing skin and muscle. Although it more commonly involves the groin, abdomen, and extremities, it may also occur in the head and neck, usually secondary to dental infection. We report a case of cervical necrotizing fasciitis arising from a dental infection and review the cause, pathophysiology, diagnosis, and treatment of this potentially lethal entity. Early detection and intervention is emphasized. Extensive surgical debridement remains the mainstay of treatment. In addition, a clarification of the various eponyms it has gone under in the past is offered.

KEY WORDS — deep neck infection, dental infection, necrotizing fasciitis.

Necrotizing fasciitis (NF) has been reported extensively in the general surgery literature.[1-3] In recent years, it has also received attention in the otolaryngology literature as more cases of NF occurring in the head and neck region are documented.[4-9] It is defined as a soft-tissue infection that causes necrosis of fascia and subcutaneous tissue while sparing skin and muscle. It has a propensity for rapid and diffuse spread, may invade vascular structures, and usually arises from a polymicrobial anaerobic or mixed aerobic-anaerobic infection. It is most commonly seen in adults, involving the groin, abdomen, and extremities, although no region of the body is exempt. It is, in these cases, usually secondary to bowel injury, trauma, or inadequate care of mundane infections such as perirectal abscesses or cutaneous ulcers. It is often seen in conjunction with a perforated viscus in postpartum patients after a traumatic delivery or in intravenous drug abusers. The highest incidence of infection occurs in patients with impaired immune systems and those with small-vessel disease, such as diabetes mellitus. Mortality rates have been reported as high as 52% and 73% in the general surgery literature.[1,2]

Necrotizing fasciitis occurs rarely in the head and neck in comparison with other regions of the body. It most commonly arises secondary to dental infections such as dental caries, gingivitis, or pulpitis, although it has been reported to occur following peritonsillar abscess as well.[8] Any infections, however, that may precipitate a deep neck infection can potentially lead to NF. These include tonsillar infections, salivary gland infections, cervical adenitis, and otologic, dermatologic, and traumatic sources. Because of the rapid and fulminant course of NF, prompt recognition is essential. The mainstays of treatment are broad-spectrum intravenous antibiotic therapy, radical surgical debridement, nutritional support, and early detection and treatment of complications.

CASE REPORT

A 30-year-old Thai man presented to the outpatient otolaryngology department with dysphagia, odynophagia, marked swelling of the left submandibular area and upper neck without fluctuance, trismus, bulging of the left lateral neck, and malaise. Two days prior to presentation, he had extractions of the lower left first and second molars by a local dentist. On admission his blood pressure was 130/90, pulse 100, temperature 39°C, hemoglobin 16, hematocrit 48, and white blood cell count 14,500 with a shift to the left. Electrolytes, urine analysis results, and findings on chest radiography were within normal limits. Blood cultures were performed, and he was subsequently prescribed 2 million units of intravenous penicillin every 4 hours.

By the second day, the patient's temperature had risen to 40°C. The swelling of the left submandibular and upper neck area had increased to involve the entire left side of his neck. An incision and drainage procedure of the left submandibular region was performed with general anesthesia. Twenty milliliters of purulent material was evacuated from the submandibular space. None was found in the parapharyngeal space. Large Penrose drains were placed in the incision. Intravenous cloxacillin, 1 g every 6 hours, was added to the antibiotic regimen.

The next day, there was no resolution of the fever, and an increased swelling of the entire neck, including the right side, was observed. It was also noted that the swelling had spread below the right clavicle to involve the anterior chest wall down to the nipple. Crepitus was found on palpation. A computed tomographic scan of the neck and chest revealed subcutaneous gas formation in the neck and right anterior chest wall. The patient was taken to the operating room for a more extensive incision and drainage procedure. Multiple parallel incisions were made in the neck and right side of the chest.

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Abundant, foul-smelling purulent material was evacuated from the neck and right anterior chest wall. In addition, the fascia overlying the muscles of the neck and chest (including the strap, sternocleidomastoid, deltoid, and pectoralis major muscles) was found to be necrotic, although the underlying muscle and overlying subcutaneous tissue and skin were uninvolved. The involved fascia was extensively debrided. A diagnosis of NF was made.

Specimens taken previously (blood, and pus from submandibular space) grew β-hemolytic group A *Streptococcus* and α-hemolytic *Streptococcus* sensitive to penicillin and chloramphenicol. *Bacteroides melaninogenicus* was also found, but no sensitivity was recorded. The cloxacillin was discontinued, and intravenous chloramphenicol 1 g every 6 hours and gentamicin 80 mg every 8 hours were added.

By the fourth postoperative day (admission day 8) the patient's fever had resolved. The chloramphenicol was discontinued. On the 10th postoperative day (admission day 14), despite overall clinical improvement, the patient was returned to the operating room for further debridement of necrotic skin seen at the edges of the incisions made previously. After this procedure, the gentamicin was discontinued, and the patient continued to receive intravenous penicillin. On day 23 of the patient's admission, an attempt was made to close the operative wound with skin grafting to avoid scar contracture. After the operation, the patient developed multiple wound infections that were successfully controlled by local wound care. The wounds subsequently healed by secondary intention without further event. The patient was discharged on admission day 32 to be followed in the outpatient department. He was prescribed oral penicillin for 2 weeks after discharge.

DISCUSSION

Necrotizing fasciitis is a clinical entity that has received various eponyms in the past.[1] This has led to some confusion over the cause and nature of the disease. It was initially described as "hospital gangrene" during the Civil War.[10,11] Meleney[12] in 1924 referred to "streptococcal gangrene" and described a synergistic interaction between *Streptococcus* and an aerobic *Staphylococcus*. Meleney felt that an arthus-type reaction was responsible for the changes seen in NF. This was based on the observed focal necrosis induced in rabbits upon subcutaneous injection of viable *Streptococcus*. McCafferty and Lyons[13] postulated that collagen necrosis was secondary to the proteolytic effect of streptokinase and staphylokinase. Schwab and Cromartie[14] and Cromartie et al[15] showed that the toxic effect of *Streptococcus* is related to the cell wall. After injecting cell wall extracts from group A *Streptococcus* into rabbits, inflammation, necrosis, and separation of dermal collagen was demonstrated. Schwab[16,17] later showed that the streptococcal toxicity resides specifically in the mucopeptide fraction of the cell wall, which was found to bind easily with connective tissue in vitro. The reaction was enhanced by streptococcal hyaluronidase.

Other terms used to describe the clinical entity of NF include "Meleney's synergistic gangrene," "bacterial synergistic gangrene," and "synergistic necrotizing fasciitis." Clostridial gangrene is a necrotizing cellulitis produced specifically by the clostridial organism but often accompanied by other organisms.[8] Although NF was originally felt to be caused primarily by aerobic agents such as β-hemolytic *Streptococcus* and *Staphylococcus aureus*, with the advent of more sophisticated anaerobic culture techniques, recent studies have shown that anaerobic bacteria play a significant role.[1,2,6,8] Most reported cases of NF suggest polymicrobial mixed aerobic-anaerobic infection. The more common anaerobic organisms seen in NF of the head and neck include *Peptostreptococcus*, *B melaninogenicus*, *Fusobacterium*, and *Clostridium*, all reflecting oral flora. Many strains of *Bacteroides* are found to be penicillin-resistant secondary to the elaboration of β-lactamase.

Gas-producing wound infections are generally produced by bacteria of the *Clostridium* group. However, nonclostridial infections have been reported to produce gas in the neck.[18] They are usually associated with less tissue necrosis than clostridial infections. The division of the clinical entity of NF into the various categories or eponyms ascribed to it in the past does not appear to be useful clinically, nor does it influence treatment. It may in fact impede or delay appropriate management. All presentations with fever and necrotizing soft-tissue infections, regardless of classification, are surgical emergencies requiring radical surgical intervention. The more general term "NF" aptly describes this disease entity and permits comparisons with results of treatment in other regions of the body.

In the initial presentation of NF, physical findings may be indistinguishable from the original infection or wound that caused it. It may occur in any part of the body, most commonly the leg, although not infrequently it will occur in the arms, genitalia, and trunk. In the head and neck, the eyelids appear to be the most common area of involvement.[5] Necrotizing fasciitis is characterized by the presence of fascial necrosis with widespread undermining of the skin and clinical manifestations of severe infection. The skin may be spared at first, but with the continued progression of the infection, thrombosis of the subcutaneous blood supply can occur, with eventual cutaneous necrosis. This is in contrast with Ludwig's angina, a more superficial infection characterized by a rapidly spreading cellulitis that may be gangrenous, involving primarily the subcutaneous tissue and soft tissue of the submental, sublingual, and submandibular spaces. Like NF, Ludwig's angina is most commonly secondary to dental infections and is often associated with chronic systemic diseases. It can also conceivably precipitate NF. It is uncommon in NF to see muscle necrosis, possibly because of the better blood supply of striated muscle. In addition, the origin of the blood supply to skeletal muscle is usually proximal to the site of infection.

The infection can spread rapidly, with involvement of an entire extremity occurring in 24 hours. If unchecked, dusky devascularized bullae may be seen on the skin, filled with dark brown fluid. Necrosis of the skin and subcutaneous tissue will follow these changes. Severe systemic effects may also be seen, including prostration, tachycardia, and fever. Marked leukocytosis will be noted. In the patient with NF of the head and neck, initial findings will relate to the portal of entry of infection, usually dental in origin. There may be crepitus in the soft tissue, although the absence of this does not rule out gas formation. Gas formation can occur in areas inaccessible to accurate palpation. Soft-tissue radiography or computed tomography (CT) scan can be useful in detecting this. Fisher et al[19] detected soft-tissue gas formation with CT in 19 of 26 patients with NF below the clavicle. Detection of this may aid in early diagnosis. Identification of specific areas in which infection has spread can be accomplished more readily preoperatively, allowing for complete and thorough drainage during the operation. If the infection has spread within the carotid sheath or into the mediastinum, earlier detection is possible. The presence of vascular thrombosis, erosion of vessels, or mediastinitis can be detected prior to operation. In our case, CT detection of gas formation in the subcutaneous tissues of the anterior chest wall allowed for a more precise assessment of areas requiring drainage.

Previously described complications for deep neck infection may also arise in NF, including airway obstruction, arterial erosion, jugular vein thrombophlebitis, mediastinitis, aspiration pneumonia, septic shock, and lung abscess.[3-6,8] A case of carotid artery thrombosis leading to acute hemiplegia in an infant has been reported.[20]

In the general surgery literature, Rouse et al[2] reported a mortality rate of 73% (20/27). Death was due to persistent wound sepsis, systemic septic complications despite local infection control, and myocardial infarction. The high incidence of chronic debilitating disease in patients with NF places these patients at risk for developing nosocomial infections and consequent multiple–organ system failure. In patients succumbing to systemic septic conditions, death was usually preceded by renal failure. Autopsies revealed multiple abscesses in the renal parenchyma. Emphasis on early surgical intervention was placed in light of the fact that 11 of 12 patients died when a delay in treatment of more than 12 hours after diagnosis occurred.[2]

Freischlag et al[1] reported a mortality rate of 52% (11/21). Again, time elapsed before the operation proved to be a factor. When it was delayed more than 24 hours after diagnosis, an overall mortality of 70% was noted. If the operation was undertaken in less than 24 hours, a 36% mortality rate was seen.[5] In a small group of patients with NF arising in the head and neck, a mortality rate of 27.5% was documented.[5]

The presence of underlying systemic disease appears to be a factor in the genesis and survival rates of NF. The presence of diabetes mellitus or arteriosclerosis was associated with a mortality rate above 80%.[2] Chronic renal failure, obesity, immunosuppression, and malnutrition were all found to influence survival rates adversely.[21-23]

TREATMENT

Effective treatment of NF is based on early recognition and surgical intervention. If a portal of entry can be identified (usually dental for infections involving the head and neck), prompt management of this focus of infection should be accomplished. A complete bacteriologic evaluation is required, including Gram's stain and aerobic and anaerobic cultures of purulent material. Appropriate transport of culture specimens and the use of proper culture media for aerobic and anaerobic culture is essential. Special efforts should be made to ensure anaerobic technique. Intravenous antibiotics effective against the common infecting organisms should be instituted. High doses of penicillin and clindamycin or chloramphenicol for penicillin-resistant *Bacteroides* are good first choices pending results of culture and sensitivity tests. If there is any reason to consider gram-negative bacterial infection, instituting a triple antibiotic regimen with the addition of an aminoglycoside is indicated.

Early radical debridement and drainage of all involved tissue remains the most important aspect of treatment. Multiple incisions are often required. In our case, serial parallel incisions were made in the neck, extending to the anterior chest wall. Subcutaneous tissue is usually edematous and may ooze a serosanguineous material upon incision. Fascial necrosis usually extends further than cutaneous involvement. Repeated debridements may be necessary. Excision to the point of bleeding tissue is a useful guide for debridement. Management of electrolyte abnormalities, in particular hypocalcemia, and control of underlying systemic illnesses are crucial. Hypocalcemia has been noted secondary to loss of calcium through saponification by necrotic fat. Attention should be paid to the overall nutritional status of the patient. Skin grafting or primary closure of open wounds may be needed after the condition resolves to avoid scar contractures.

SUMMARY

Necrotizing fasciitis is a potentially serious complication of routine infections in the head and neck. It usually arises from a dental focus of infection, although other infected areas of the head and neck can lead to NF, particularly in patients with chronic systemic debilitating illnesses such as diabetes mellitus. For those patients suspected of having NF, a CT scan is an important adjunct to clinical impression and will aid in assessing the full extent of the infection. It will also assist in the earlier detection of complications such as involvement of the carotid sheath or mediastinitis. Appropriate cultures and Gram's stains should be performed. As NF is polymicrobial in nature, with mixed aerobic and anaerobic organisms present, initial intravenous antibiotics should be broad-spectrum and include high doses of penicillin and clindamycin or chloramphenicol for penicillin-resistant organisms. The mainstay of treatment is early radical debridement and drainage of all infected tissue. Only with prompt surgical intervention can complications and mortality be reduced.

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HYDROCORTISONE DELAY OF TISSUE REPAIR OF EXPERIMENTAL TYMPANIC MEMBRANE PERFORATIONS

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The effects of topically applied hydrocortisone on experimental tympanic membrane (TM) perforations in rats were evaluated by otomicroscopy and light microscopy. Standardized TM perforations, occupying the whole upper rear quadrant, were performed, and a 2% hydrocortisone suspension (CORT) was applied once daily for 10 consecutive days. Application of CORT caused a delayed healing pattern, and even at 1 month only 2 of 12 perforations had healed. The keratinizing squamous epithelial cells of the TM appeared hypertrophic, whereas hyperplasia, characterizing a nontreated healing TM perforation, was less prominent. The connective tissue layer of the CORT-treated TM was invaded by abundant inflammatory cells, mainly polymorphonuclear leukocytes. Also, when applied to an intact TM, CORT caused hypertrophy of the epidermal cells and an inflammatory reaction within the TM.

KEY WORDS — hydrocortisone, keratinizing squamous epithelium, perforation, tympanic membrane.

INTRODUCTION

Glucocorticoids, both alone and combined with antibiotics, are widely used in topical treatment of various ear diseases. Steroid-containing drugs are also used to prevent swelling and postoperative infections in otosurgery. Adverse effects of topically applied corticosteroids in the ear are sparsely reported in the literature.[1,2] In dermatology, however, several unwanted side effects of topical corticosteroid therapy are described,[3] of which atrophy is the most common. Recently, in an experimental study[4] it was noted that minute perforations of the tympanic membrane (TM) showed a considerably delayed healing pattern when hydrocortisone was applied.

In the present study we purposed to characterize the structural changes involved in the altered healing pattern of experimental TM perforations following repeated topical applications of hydrocortisone. The effects of glucocorticoids on an intact TM were also evaluated.

MATERIALS AND METHODS

The experimental design is shown in Fig 1. Thirty-one male albino Sprague-Dawley rats, weighing about 300 g, with normal TM status were divided into two groups.

Group A. In 16 animals, myringotomy was performed with a myringotomy lancet in both right and left TMs under an otomicroscope. The perforation was roughly 1.5 mm in diameter and occupied the whole posterior upper quadrant of the TM, from the handle of the malleus to the vicinity of the fibrocartilaginous ring (Fig 2).

Twenty-four TMs (16 right, 8 left) were exposed daily for 10 consecutive days to a 2% suspension of hydrocortisone (CORT) micronized in sterile water. The remaining 8 left ears were exposed to sterile water (SW) only.

Approximately 20 µL CORT and SW, respectively, was applied with a syringe on the perforation borders. The substance covered the surrounding TM surface, but also entered the middle ear cavity. At day 10, day 20, day 30, and day 60 after the initial application, groups of animals (four, four, five, and three, respectively), were killed painlessly by an intraperitoneal overdose of a pentobarbiturate (Mebumal). Throughout the 2-month period, the animals were killed at intervals ranging from daily to twice a week, in order to examine the TM status and establish the day on which the perforation eventually closed.

For the otomicroscopic examination of the TMs, myringotomy, and application of the substance, the animals were anesthetized by intravenous injection of sodium methohexital (Brietal, 50 mg/mL) via a tail vein.

Group B. In 15 animals the CORT was applied once daily on 5 consecutive days, onto the surface of the intact TM in the right ear via a cannula through an ear speculum. Approximately 20 µL was deposited, and the excess substance was left in the ear canal. The left ears served as controls and were exposed in the same way to SW only (Fig 1). On days 7, 21, and 60 after the initial application, five animals were killed painlessly according to the procedure outlined for group A.

Light Microscopic Procedure. At death the rats

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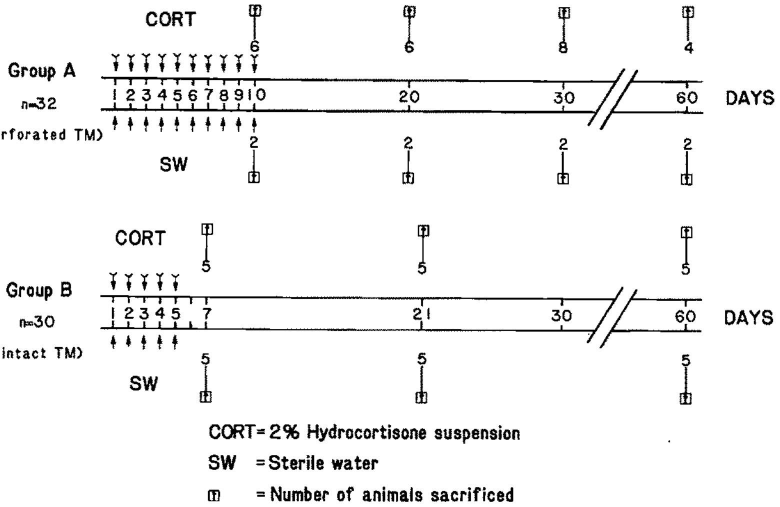


Fig 1. Schematic outline of experimental design. Arrows — applications of substance.

were decapitated, and the tympanic bulla was opened. Through this opening a fixative solution containing 3% glutaraldehyde in 0.1 mol/L sodium cacodylate buffer with 4% polyvinylpyrrolidone added was instilled, and the skulls were immersed for at least 24 hours. After fixation the TMs were dissected, rinsed in buffer, and postfixed in 1% osmium tetroxide in cacodylate buffer. After dehydration in increasing concentrations of ethanol, the specimens were embedded in Epon. Semithin sections were cut on a Porter-Blum ultramicrotome, stained with toluidine blue, and then examined under a light microscope.

RESULTS

GROUP A (PERFORATED TYMPANIC MEMBRANES)

Otomicroscopic Observations. The CORT-treated perforations showed a markedly delayed healing pattern compared with those treated with SW only (Fig 3). On day 10, all perforations of both groups were open, but the SW-treated perforations were reduced to approximately half of their initial size. All SW-treated perforations closed between days 12 and 17 (median, day 13), whereas the CORT-treated perforations showed no sign of healing. On day 20, 17 of 18 CORT-exposed TM perforations remained open. On day 30, 10 of 12 CORT-treated perforations had still not healed. Two months after the start of the experiment, 2 of 4 CORT-exposed perforations were still open (Fig 4).

Light Microscopic Observations. On day 10 (Fig 5), the perforation border of the SW-treated perforations showed a marked hyperplasia of the stratified keratinizing epithelium (Fig 5A,B). The border of the CORT-treated perforation was also thickened (Fig 5C-E). However, this thickening appeared to be due mainly to hypertrophy and not to hyperplasia. The CORT-induced hypertrophy also engaged the nonperforated half of the eardrum (Fig 5E). In the connective tissue layer of the perforation border, the occurrence of inflammatory cells, as well as the orientation of the fibroblasts, differed between the CORT- and SW-treated perforations. The CORT-treated tissue was invaded by abundant inflammatory cells, mainly polymorphonuclear leukocytes, whereas the control tissue contained few inflammatory cells. The inner epithelial lining was similar in the two groups.

By day 20 (Fig 6), all SW-treated perforations had closed. The keratinizing squamous epithelium of the healed TMs was remarkably reduced in thickness (Fig 6A). Fibroblasts in the connective tissue layer of the SW-treated perforations appeared to be more oriented with their long axes parallel to the surface of the drum, compared with the CORT group. A few inflammatory cells and occasional mast cells were present. In contrast, 17 of 18 of the CORT-treated TM perforations remained open, and their structural appearance resembled that of day 10 (Fig 6B,C). A large number of inflammatory

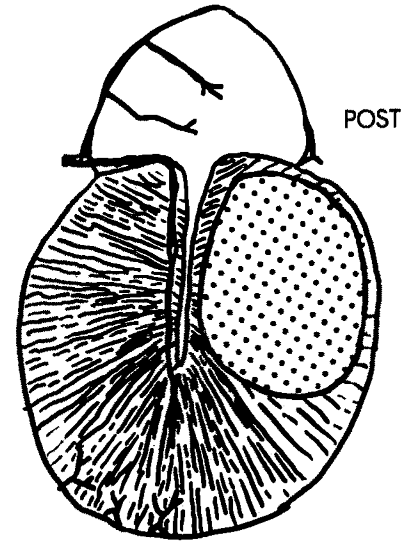


Fig 2. Schematic drawing of left tympanic membrane from rat, showing location and size of perforated area (dotted area) in upper posterior (POST) quadrant.

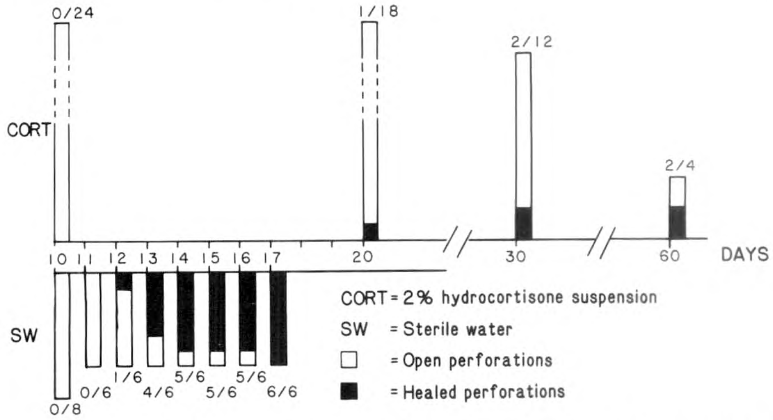


Fig 3. Day of closure of tympanic membrane perforations.

cells were seen in a richly vascularized connective tissue layer. Furthermore, fibroblasts were numerous, and patches of bonelike tissue were seen.

On day 30 (Fig 7), the SW-treated TMs were further reduced in thickness compared with day 20 TMs (Fig 7A,B). The healed areas showed signs of an organized fibrous layer with few fibroblasts. No inflammatory cells were seen. The keratinizing squamous epithelium appeared normal. On day 30, 10 of 12 CORT-treated perforations were still open, though reduced in size. Healing appeared to proceed mainly from the annular area of the eardrum and not from the mallear side (Fig 7C). A rather thin keratinizing squamous epithelial cell layer rested on connective tissue rich in less-well-oriented fibroblasts. Some specimens contained sclerosislike patches in the connective tissue.

At 2 months (day 60) the healed SW-treated perforations appeared normal. Two of four CORT-treated perforations were closed. The keratinizing squamous epithelium appeared thin in all cases (Fig 8). The connective tissue layer was still thickened, fibrotic, and well vascularized. There were few inflammatory cells. Islets of keratinizing squamous epithelium remained within the connective tissue (Fig 8B).

GROUP B (INTACT TYMPANIC MEMBRANES)

Otomicroscopic Observations. The SW-exposed TMs were all normal. On days 7 and 21, the TMs exposed to CORT appeared less transparent. In some specimens, crusts of wax and dried CORT remained on the TM surface. No perforations were noted. The pars flaccida remained in the normal position, with no sign of effusion material medial to it.

Light Microscopic Observations. Topical application of SW on the intact TM surface did not cause any structural changes at any time (Fig 9A,B). In the intact TMs exposed to CORT, the following changes were noted.

On day 7 (Fig 9C-E), the keratinizing squamous epithelium of the TMs exposed to CORT was thickened and showed hypertrophy. Dense aggregations of keratin covered the drum. The fibrous layer remained unchanged. Attached to the inner epithelial lining were abundant polymorphonuclear leukocytes. These aggregates of inflammatory cells were more prominent in the less-vascularized, transparent portions of the pars tensa. In two of five specimens a pronounced inflammatory reaction with aggregations of abundant inflammatory cells was located within the TM tissue, as well as covering both its epithelial surfaces (Fig 9E).

On day 21, restricted areas with a hypertrophic keratinizing stratified epithelium were present. Occasional macrophages with dense inclusion bodies

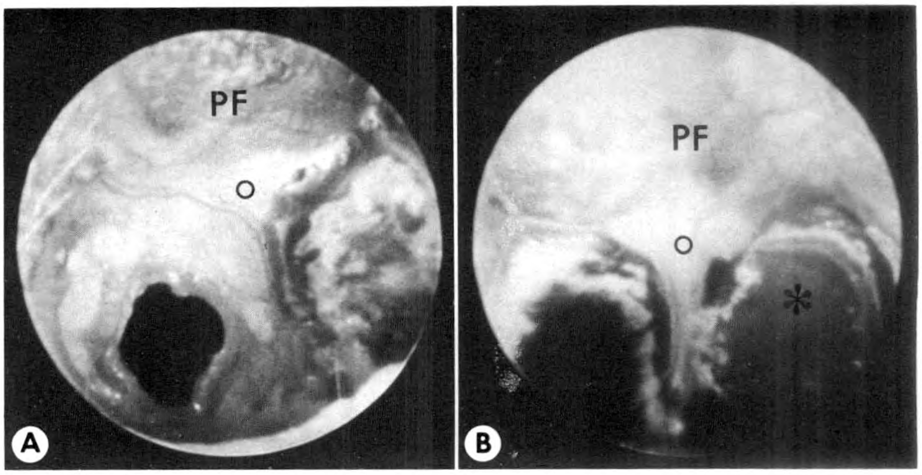


Fig 4. Endoscopic micrographs of treated tympanic membrane (TM) perforations, which were performed in posterior half of TM. Circle — handle of malleus, PF — pars flaccida. A) Two percent hydrocortisone suspension (CORT)-treated rat TM at 2 months. Perforation is reduced in size, but remains open. Handle of malleus has dilated manubrial vessels. B) Sterile water-treated TM at 15 days. Healed area (asterisk) is less transparent than normal TM.

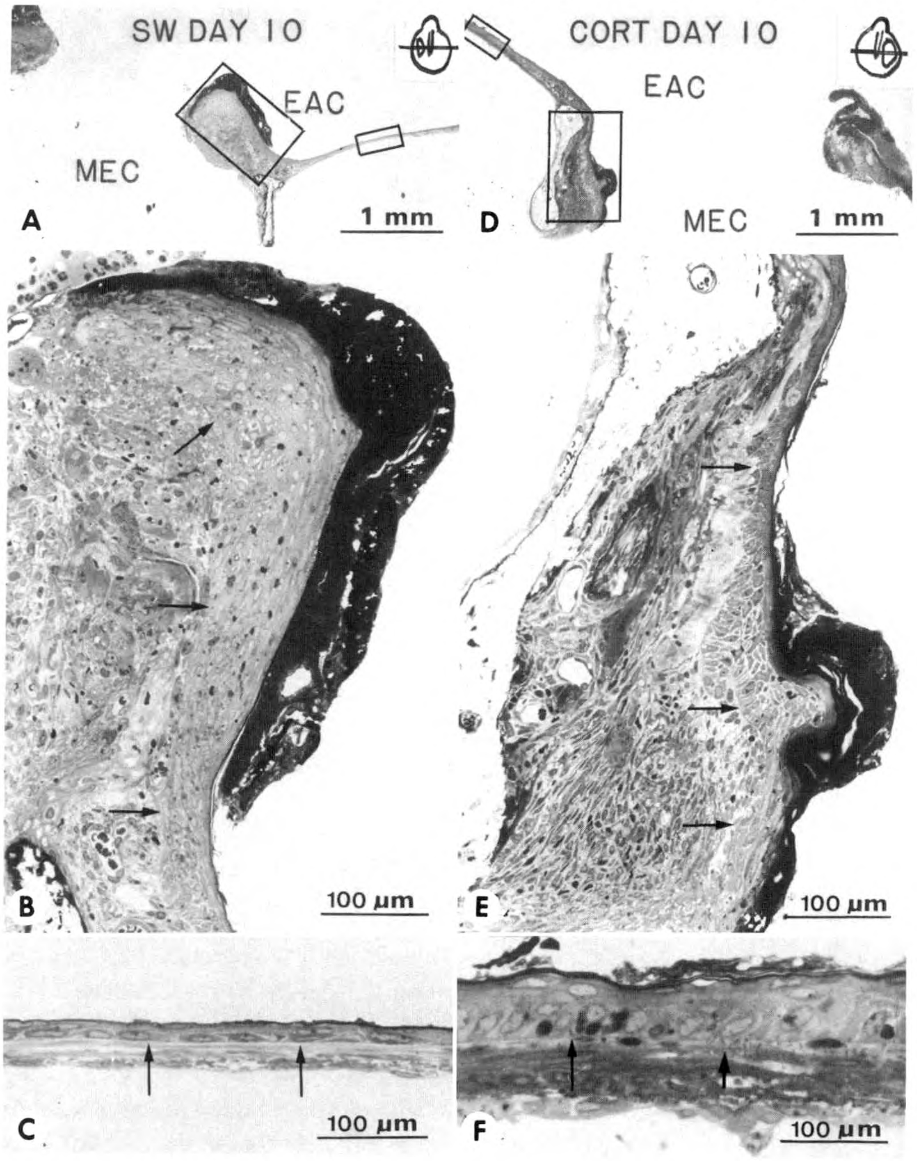


Fig 5. Light micrographs of semithin plastic sections of TM perforations on day 10 (toluidine blue). A-C) Sterile water (SW)–exposed perforation. A) Survey picture (original x16). MEC — middle ear cavity, EAC — external auditory canal. Inset) Level of TM at which it was sectioned. B) Detail of A (large box) at perforation border (original x175). Arrows — junction between keratinizing squamous epithelium and connective tissue layer. C) Small box in A (original x175). Portion of TM anterior to handle of malleus, ie, nonperforated half. Arrows as in B. D-F) CORT-treated perforation. D) Survey picture (original x16). Abbreviations and inset as in A. E) Detail of D (large box) at perforation border (original x175). Arrows as in B. F) Portion of TM anterior to handle of malleus, ie, nonperforated half (small box in D) (original x175). Arrows as in B.

were noted in the fibrous layer.

On day 60 (Fig 9F,G), the TM structure appeared normal, except for a few areas with a thickened hypertrophic keratinizing epithelium.

DISCUSSION

The pattern of epithelial migration during the healing of a perforated TM has been extensively studied in experimental and clinical materials.[5-10] Under these controlled conditions, both the healing rate and the structural events can be easily distinguished.

Experimental TM perforations are closed by the proliferation of a hyperplastic keratinizing squamous epithelium advancing ahead of ingrowing connective tissue. The keratinizing squamous epithelium is guided by a spur of keratin. In this manner, central perforations of a size similar to that made in the present study closed within 9 to 12 days.[10] Following closure of the perforation, the hyperplasia of the keratinizing squamous epithelium ceased rapidly, and the epithelium regained its normal thickness within 1 to 2 days. In contrast, the connective tissue layer remained thickened for several months.

In comparison with the normal healing pattern, the exposure of TM perforations to CORT delayed healing significantly. Perforations still remained open after 1 month. The treatment also induced quite different structural alterations of the keratinizing squamous epithelium. Instead of a marked hyperplasia of the keratinizing squamous cells at the perforation border, the CORT-treated TMs showed hypertrophy without any striking difference in the number of cell layers. Keratinocytes exhibiting mitotic figures, frequent during normal healing, were only occasionally observed in the CORT-treated tissue. It appears that one factor involved in the delayed healing pattern following cor-

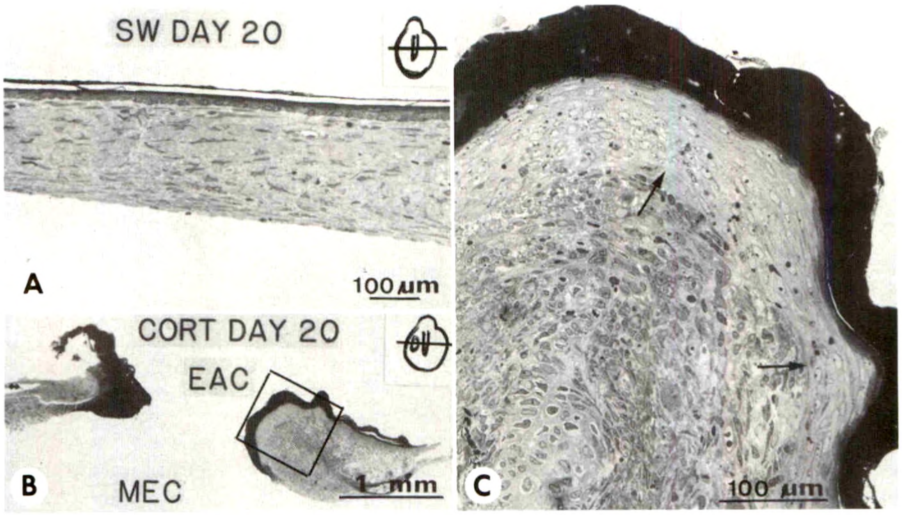


Fig 6. Light micrographs of semithin plastic sections of TM perforations on day 20 (toluidine blue). A) Sterile water (SW)-exposed perforation (original x70). Note thin keratinizing stratified squamous epithelium. Fibroblasts are oriented parallel to surface of TM. Inset) Level of TM at which it was sectioned. B,C) CORT-treated perforation. B) Survey picture (original x16). EAC — external auditory canal, MEC —middle ear cavity. Inset) Level of TM at which it was sectioned. C) Detail of B (box) (original x175). Arrows —junction between keratinizing squamous epithelium and connective tissue layer.

ticosteroid treatment is a reduced proliferation of the squamous epithelial cells. It is known that corticosteroids are capable of inhibiting cell division[11] and can restrict protein[11-13] and mucopolysaccharide synthesis.[14] In the present study the keratinocytes hypertrophied during CORT treatment. The increase in cell size was observed not only at the perforation border, but throughout the whole tympanic membrane. Corticosteroids are able to stimulate the synthesis of various enzymes,[15] and the hypertrophy could reflect an increased activity of individual cells, eg, an accelerated synthesis of keratin.

From long-term treatment with glucocorticoids on skin, it is established that steroids can exert a profound effect on several connective tissue components, eg, collagen, elastin, glycosaminoglycans, and fibronectin.[16] It is also known that this substance can influence the fibrillogenesis of collagen.[17] In consequence the glucocorticoids have an inhibitory effect on wound healing and present a constant danger of wound dehiscence.[15] The effect on the connective tissue in the present study is noticeable and should also contribute to the delayed healing pattern. Lehmann et al[18] studied corticosteroid-dependent atrophy of human skin and found a flattening of the dermoepidermal junction and a reorganization of the three-dimensional architecture of the dermis. The latter finding was attributed to resorption of the ground substance, resulting in smaller interfibrillar spaces between the collagen and elastic fibers. One of the major components of the ground substance is hyaluronan (hyaluronic acid; HA). Steroids have the capacity to reduce the synthesis of this matrix substance.[19,20] In this context it is interesting that topical application of HA onto experimental perforations enhances the healing rate.[21,22] Treatment with HA also improves the restoration of the fibrous connective tissue layer, resulting in less opacity and less structural alteration of the scar.[23] The accelerated healing rate was suggested to depend on the physicochemical properties of HA that appeared to make it easier for the keratinizing squamous epithelial cells to migrate and bridge the perforation. Suppression of HA synthesis by the CORT treatment could also explain the delayed healing observed in the present study.

It is noteworthy that the healing rate of the per-

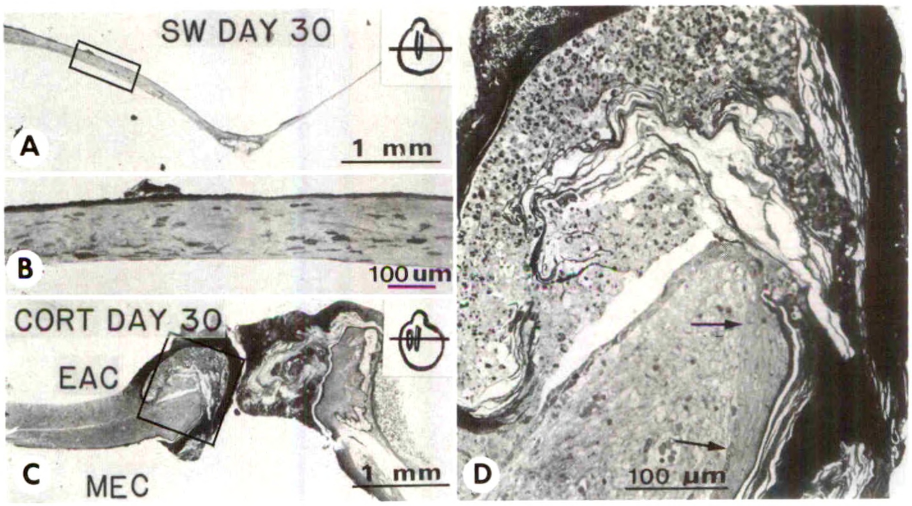


Fig 7. Light micrographs of semithin plastic sections of TM perforations on day 30 (toluidine blue). A,B) Sterile water (SW)-exposed perforation. A) Survey picture (original x16). Inset) Level of TM at which it was sectioned. B) Detail of A (box) (original x175). Connective tissue layer contains small numbers of fibroblasts. C,D) CORT-treated perforation. C) Survey picture (original x16). Advancing borders of perforation with masses of keratin are almost bridging gap. EAC — external auditory canal, MEC — middle ear cavity. Inset) Level of TM at which it was sectioned. D) Detail of C (box) (original x175). Arrows — junction between keratinizing squamous epithelium and connective tissue layer.

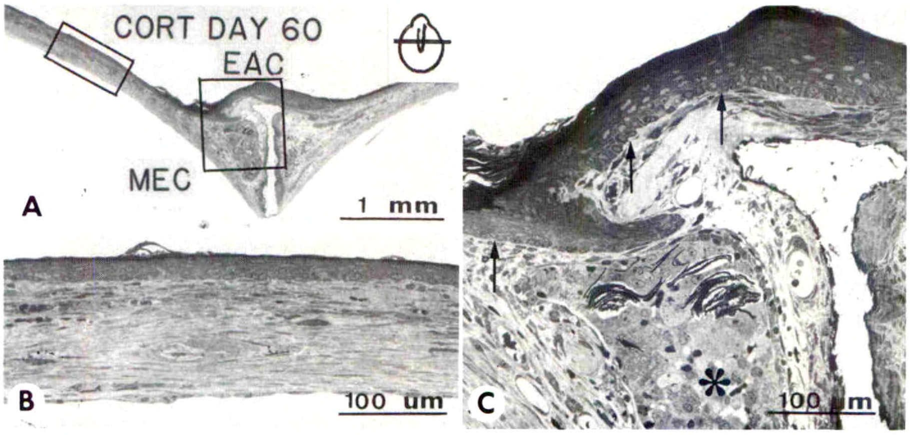


Fig 8. Light micrograph of semithin plastic sections of CORT-treated TM perforations on day 60 (toluidine blue). A) Survey picture (original x16). EAC — external auditory canal, MEC —middle ear cavity. Inset) Level of TM at which it was sectioned. B) Detail of A (small box) through healed area (original x175). C) Detail of A (large box) close to mallear handle (original x175). Island of keratinizing squamous epithelium remains within TM connective tissue (asterisk). Arrows — junction between keratinizing squamous epithelium and connective tissue layer.

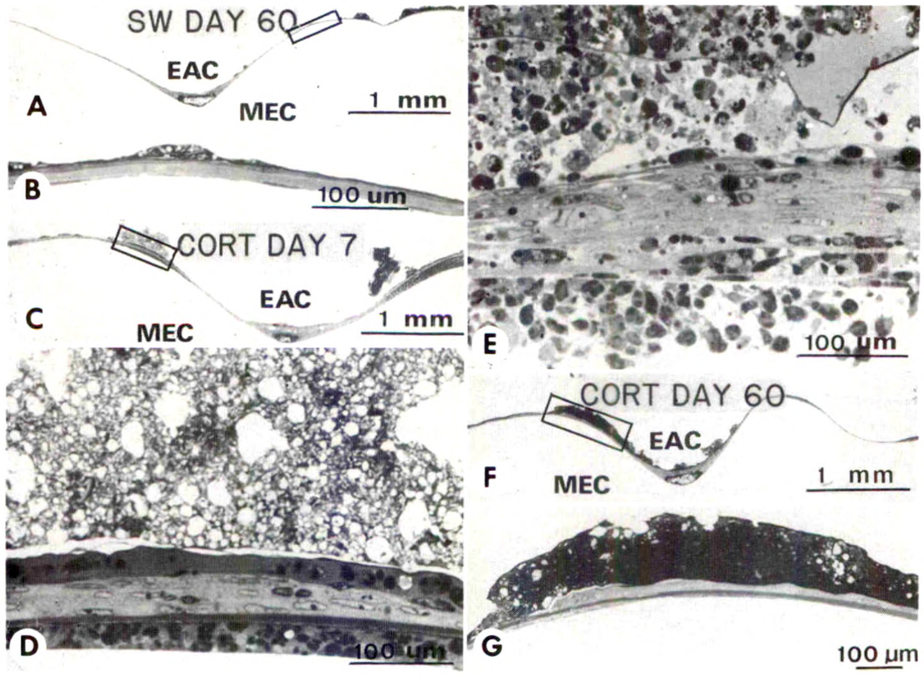
forated control TM on the contralateral side was also delayed. This could be explained by a systemic effect of CORT, as excess substance trapped in the middle ear cavity could escape through the eustachian tube, be swallowed, and be absorbed from the gastrointestinal tract.

Interestingly, the healing process seemed to take place predominantly from the annular side of the drum, and not from the mallear side. This contrasts with our present knowledge of the migratory pattern of the TM epidermal cells.[24] However, in the wound condition it is likely that the epithelium of the ear canal could contribute to the closure of the perforation. The three-layered nature of the keratinizing squamous epithelium was rapidly reestablished in the control group, whereas the connective tissue layer remained thickened for a considerable time. In contrast, in the few closed perforations in the CORT group, the keratinizing squamous epithelium remained hypertrophic throughout the 2-month observation period.

It is remarkable that the keratinizing squamous epithelium of the intact TM following exposure to CORT showed structural changes similar to those of the perforated TMs. The hypertrophic keratinizing cells were covered by a dense carpet of keratin. Abundant inflammatory cells were attached to the inner epithelial lining and were also noted in the otherwise unchanged fibrous layer. However, with an intact TM, the structural changes affecting the connective tissue were less advanced, and the TM had returned to almost normal after 2 months.

In tympanoplasty, steroid-soaked dressings are frequently used, and corticosteroid ointments have in fact been utilized in acute traumatic perforations of the eardrum. In both these conditions a rapid re-epithelialization of the wound area is a prerequisite for good end results. If local application of cortisone in humans impairs the healing process in the same way as observed in the present experimental study, its clinical use should obviously be restricted.

Fig 9. Light micrographs of semithin plastic sections of intact TMs (toluidine blue). A,B) Sterile water (SW)–exposed TM on day 60. A) Survey picture (original x16). EAC — external auditory canal, MEC — middle ear cavity. B) Detail of A (box) (original x175). C-E) CORT-treated TM on day 7. C) Survey picture (original x16). MEC — middle ear cavity, EAC — external auditory canal. D) Detail of C (box) (original x175). Hypertrophy of keratinized squamous epithelium and accumulation of inflammatory cells are seen on inner surface of TM. E) Heavy masses of inflammatory cells are noted on both inner and outer surface of severely altered TM (original x175). F,G) CORT-treated TM on day 60. F) Survey picture (original x16). MEC — middle ear cavity, EAC — external auditory canal. G) Detail of F (box) (original x175). Note discrete areas of still-thickened keratinizing epithelium.



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MORPHOLOGIC AND BIOCHEMICAL STUDY OF VASCULAR PERMEABILITY OF THE MIDDLE EAR MUCOSA IN EXPERIMENTAL OTITIS MEDIA

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The vascular permeability of the middle ear mucosa of chinchillas was examined by light and electron microscopy using horseradish peroxidase (HRP). Two kinds of experimental otitis media were used: serous otitis media (SOM) produced by eustachian tube obstruction and purulent otitis media (POM) produced by inoculation with *Streptococcus pneumoniae* type 7F. Normal mucosa showed no leakage of HRP. In SOM, vessels were dilated and tortuous, but they did not show HRP leakage. In POM, vessel leakage of HRP was extensive. Biochemically, we measured the middle ear effusion-to-serum ratio of both albumin and α2-macroglobulin by an immunodiffusion method. The ratios of the two marker proteins for vascular permeability were significantly higher in POM than in SOM. This suggests that POM increases vascular permeability to a higher degree than SOM, and morphologic findings in the middle ear mucosa correlate with the biochemical composition of the middle ear effusion.

KEY WORDS — horseradish peroxidase, middle ear mucosa, otitis media, vascular permeability.

INTRODUCTION

Several biochemical studies have shown that alteration of vascular permeability appears to be an important factor in the pathogenesis of otitis media.[1-4] On the other hand, there has been little direct morphologic evidence of vessel involvement. To the best of our knowledge, only Hiraide and Paparella[5] and Hiraide and Eriksson[6] have reported that vascular permeability increased in the middle ear mucosa after eustachian tube obstruction (ETO)[5] or in the presence of negative pressure.[6] In their study, they used the classic method of carbon particle vascular labeling. They did not discuss the mechanism of increased vascular permeability at the ultrastructural level, nor did they examine purulent otitis media (POM).

Horseradish peroxidase (HRP) has been widely used as a tracer to examine vascular leakage under light and electron microscopes.[7-10] In the present study, the vascular permeability of normal middle ear mucosa and mucosa affected by experimental otitis media was examined with use of HRP. Furthermore, we attempted to study the correlation between the biochemical composition of the middle ear effusion (MEE) and the morphologic findings in the middle ear mucosa.

MATERIAL AND METHODS

A total of 28 healthy chinchillas, weighing 350 to 740 g, were used in the present study. They were purchased from a single supplier and kept on a standard diet.

As a control group, five normal animals were injected with HRP in the same way as the otitis media groups.

For the serous otitis media (SOM) group, 10 animals were used. After anesthesia with ketamine hydrochloride (20 mg/kg, intramuscularly), an incision was made in the middle of the soft palate. The pharyngeal orifice of the eustachian tube was visualized, and small pieces of sterile Silastic sponge were placed into the orifice to obstruct the eustachian tube completely. The incision in the soft palate was sutured. Five animals were killed painlessly 1 day after ETO, and the others 1 week after ETO.

For the POM group, 10 animals were used. After anesthesia with ketamine hydrochloride, POM was produced by direct inoculation of type 7F *Streptococcus pneumoniae* (20 colony-forming units per ear) into the bulla. Five animals were killed painlessly 1 day after inoculation, and the others 1 week after inoculation.

Morphologic Study. Control and experimental animals were anesthetized with an intraperitoneal injection of 60 mg/kg pentobarbital sodium. They were injected intravenously with 60 mg/kg of HRP (type II, Sigma) and killed painlessly by decapita-

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From the Department of Otolaryngology, University of Minnesota Medical School, Minneapolis, Minnesota. Supported by National Institutes of Health grants NS 14538 and NS 12125. This study was performed in accordance with the PHS Policy on Humane Care and Use of Laboratory Animals, the NIH *Guide for the Care and Use of Laboratory Animals*, and the Animal Welfare Act (7 U.S.C. et seq.); the animal use protocol was approved by the Institutional Animal Care and Use Committee (IACUC) of the University of Minnesota Medical School.

Presented at the meeting of the American Academy of Otolaryngology–Head and Neck Surgery, Washington, DC, September 25-29, 1988.

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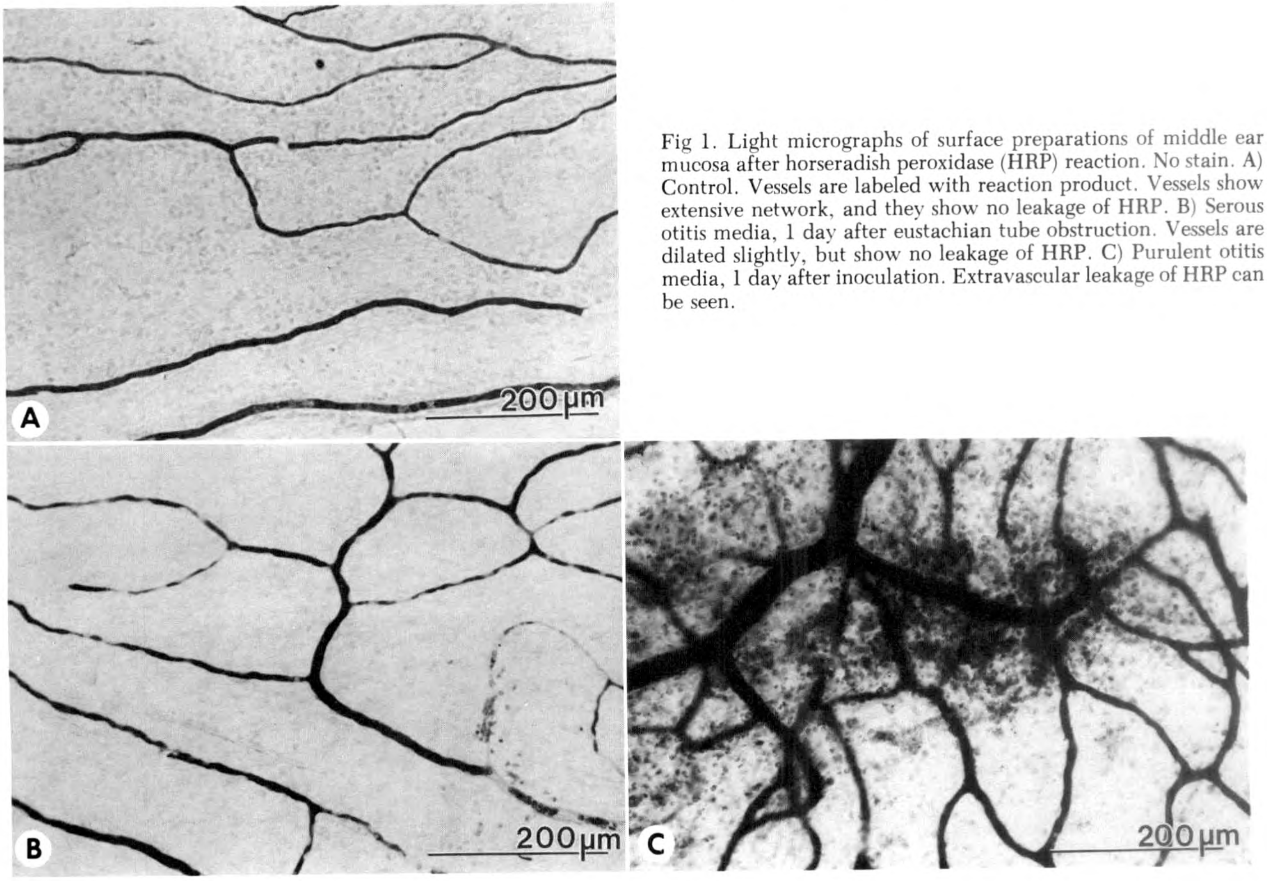

Fig 1. Light micrographs of surface preparations of middle ear mucosa after horseradish peroxidase (HRP) reaction. No stain. A) Control. Vessels are labeled with reaction product. Vessels show extensive network, and they show no leakage of HRP. B) Serous otitis media, 1 day after eustachian tube obstruction. Vessels are dilated slightly, but show no leakage of HRP. C) Purulent otitis media, 1 day after inoculation. Extravascular leakage of HRP can be seen.

tion 10 minutes after injection. The bulla was opened and fixed by perfusion with 2% glutaraldehyde in 0.1 mol/L phosphate buffer, pH 7.3, for 30 minutes. The middle ear mucosa was removed as a surface preparation in ice-cold phosphate buffer with 5% sucrose under a dissecting microscope. Middle ear mucosa of the hypotympanic bulla was harvested at a point some distance from the eustachian tube in order to avoid vessel leakage due to any mechanical damage caused by tubal obstruction.[7] The pieces of middle ear mucosa were preincubated in 0.05 mol/L Tris buffer, pH 7.6, for 30 minutes and then incubated in Hanker-Yates incubation medium (100 mL Tris buffer, pH 7.6, plus 150 mg Hanker-Yates reagent plus 0.1 mL of 30% H_2O_2) for 30 minutes at room temperature.[10] They were then postfixed in 1% ice-cold osmium tetroxide for 1 hour, rinsed in phosphate buffer, dehydrated in a series of ethyl alcohols, and embedded in methyl methacrylate (Medcast). Ultrathin sections for electron microscopy were stained with uranyl acetate and lead citrate and examined on a JEOL 100 electron microscope.

Specimens for surface preparation were mounted on the slide glasses with glycerin and examined on a light microscope.

In order to examine the endogenous peroxidase activity, one animal in each group was killed painlessly with saline injection instead of HRP and processed in the same way as mentioned above.

Biochemical Study. Middle ear effusion was sampled via the epitympanic bulla 1 week after ETO (n = 5) or inoculation (n = 5). A blood sample was collected by cardiac puncture. In all SOM cases, culture of MEE was negative for bacteria. All MEEs sampled were centrifuged to remove particulate materials, and the clear fluid was stored at -70°C until use. Albumin levels in both MEE and plasma were measured by a single radial immunodiffusion method using a specific rabbit anti chinchilla albumin antiserum.[11] Alpha2-macroglobulin (α2-M) levels in both MEE and plasma were measured by an electroimmunodiffusion method using a specific rabbit anti chinchilla α2-M antiserum.[12] The values were expressed as the ratio of MEE to plasma concentrations.

RESULTS

Control. The middle ear mucosa after HRP reaction showed the vascular network (Fig 1A). The middle ear mucosa was thin, and HRP was confined to the vessel lumen (Fig 2A).

Serous Otitis Media. In the experiment 1 day after ETO, vessels were dilated slightly and subepithelial tissue was thickened. No HRP was detected outside the vessel lumen (Figs 1B and 2B). In the middle ear mucosa 1 week after ETO, labeled vessels were dilated and tortuous, but they did not

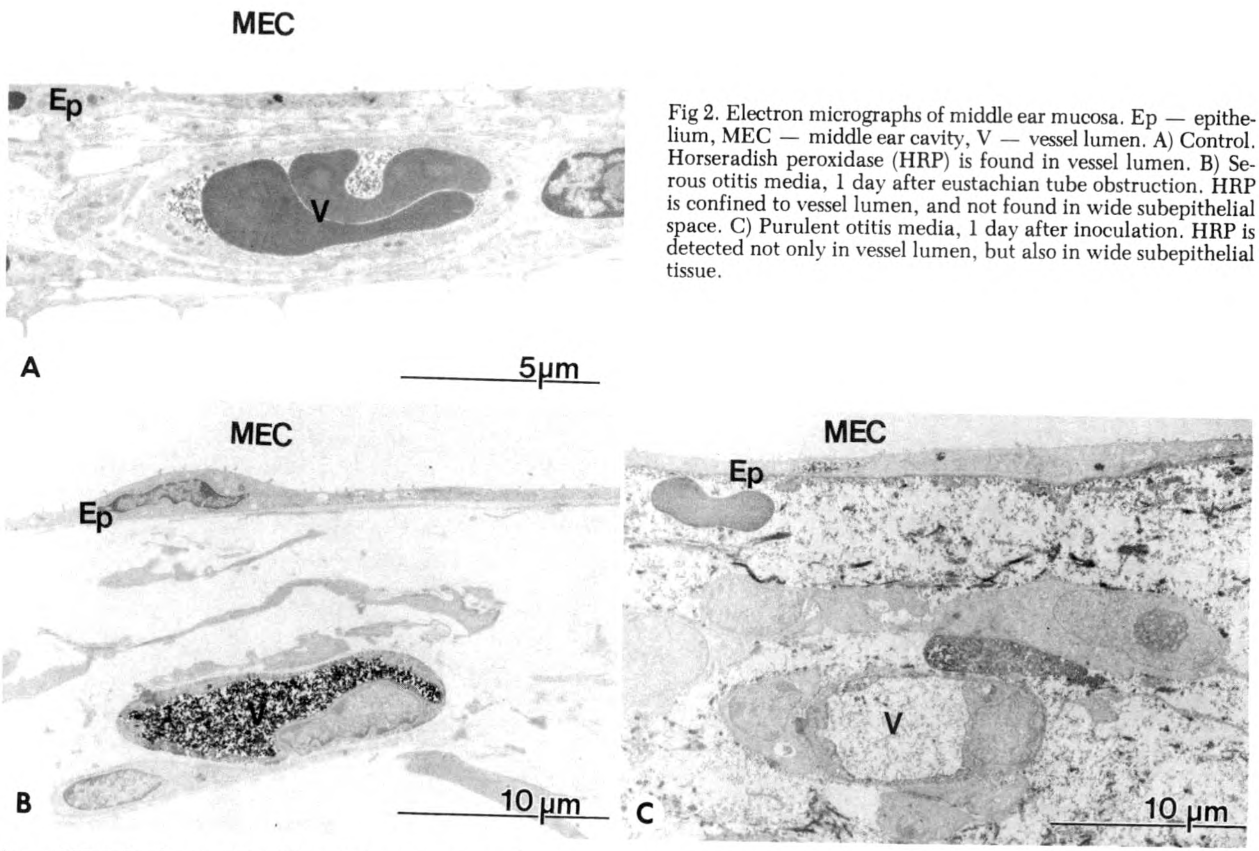

Fig 2. Electron micrographs of middle ear mucosa. Ep — epithelium, MEC — middle ear cavity, V — vessel lumen. A) Control. Horseradish peroxidase (HRP) is found in vessel lumen. B) Serous otitis media, 1 day after eustachian tube obstruction. HRP is confined to vessel lumen, and not found in wide subepithelial space. C) Purulent otitis media, 1 day after inoculation. HRP is detected not only in vessel lumen, but also in wide subepithelial tissue.

show HRP leakage (Fig 3A). There were a few inflammatory cells and an excess of fibrocytes in the thickened subepithelial tissue (Fig 4A).

Purulent Otitis Media. In the middle ear mucosa 1 day after inoculation, vessels contained intense HRP reaction product, and leakage of HRP was detected (Fig 1C). Electron microscopic observation revealed neither hyperplasia nor metaplasia of epithelial cells. Inflammatory cells such as neutrophils occasionally were seen in the subepithelial space. Reaction product of HRP was scattered throughout the extracellular subepithelial tissue (Fig 2C). In the middle ear mucosa 1 week after inoculation, vessels showed intensive HRP reaction product (Fig 3B). Cuboidal and columnar epithelial cells and many polymorphonuclear neutrophils were also found. Reaction product was observed in the subepithelial tissue and in the intercellular spaces between epithelial cells (Fig 4B). No HRP was observed in the area of tight junctions between epithelial cells facing the middle ear cavity (Fig 5).

Sections obtained from control and experimental animals with an injection of saline instead of HRP did not show any reaction product in the intercellular spaces. Endogenous peroxidase activity was found in the inflammatory cells and sometimes in the fibrocytes (Fig 6).

Biochemical analysis 1 week after ETO or inoculation showed that MEE/plasma ratios of both albumin and α2-M were significantly higher in POM than in SOM (Fig 7).

DISCUSSION

In the present study, normal middle ear mucosa of chinchilla did not show HRP outside the vessel lumen. We used the bulla mucosa instead of the mucosa near the tubal orifice, because we were afraid that mechanical tubal obstruction could directly affect the middle ear mucosa near the eustachian tube and cause leakage of HRP. Haye and Vegge[13] reported that middle ear mucosa near the tubal orifice of guinea pigs sometimes showed the reaction product outside vessels, and that the bulla mucosa rarely did. They also mentioned that fenestrated capillaries in the bulla mucosa were very rare. It appears that HRP leakage does not take place in the normal middle ear mucosa, as shown in the present study.

Hiraide and Paparella,[5] using the carbon particle labeling method, reported that vascular leakage of carbon particles in guinea pig middle ear mucosa reached the maximum level between 1 and 2 days after SOM was induced. In the present study, we observed no HRP leakage in the middle ear mucosa either 1 day after ETO or 1 week after ETO. The carbon labeling method is the classic way to observe vessel leakage. In this method, carbon particles attached to the vascular wall and the labeling of the basal lamina are considered to show leakage.[14] On

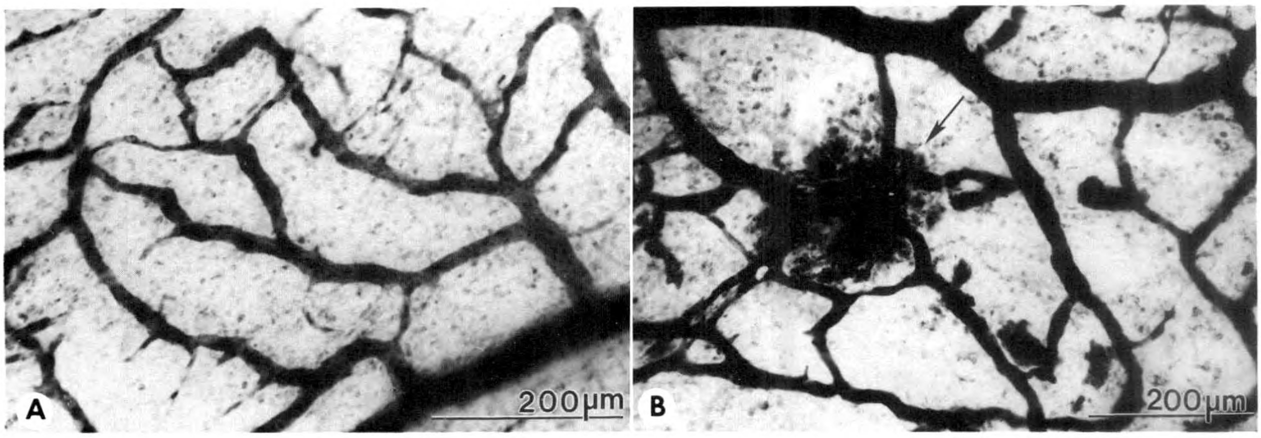

Fig 3. Light micrographs of surface preparation of middle ear mucosa after horseradish peroxidase reaction. No stain. A) Serous otitis media, 1 week after eustachian tube obstruction. Vessels are dilated and tortuous, but show no horseradish peroxidase leakage. B) Purulent otitis media, 1 week after inoculation. Vessels are prominently dilated and tortuous. Leakage spot can be seen (arrow).

the other hand, the HRP method indicates the localization of reaction product of HRP outside the vessel lumen. Therefore, the discrepancy between the results of the two studies could be due to the methods employed.

Although there was massive edema in the middle ear mucosa of the SOM animals, vascular leakage of HRP was not detected in the subepithelial tissue. The reason remains unknown, but there are several possibilities. 1) Venostasis and lymphostasis occurred in the ETO models, and they induced transudation from the vessels (the HRP method cannot illustrate transport of water and small substances between tissue and lumen). 2) At the time HRP was administered, the concentration of protein equilibrated between vessel lumen and perivascular space, and movement of HRP across the epithelium did not occur. 3) The HRP actually leaked out of vessels, and then was distributed in the subepithelial tissue to a point at which detection of HRP reaction product was impossible. Since HRP was detectable in the edematous spaces of middle ear mucosa from POM animals, the last possibility seems unlikely.

In POM, a large amount of HRP was observed in the subepithelial space. The degree of extravasation of HRP was not compared between the 1-day and 1-week POM groups, because the HRP method is a qualitative rather than a quantitative method, as shown in most morphologic tracer methods. The possible pathways of HRP across the vascular endothelium are 1) through fenestrae, 2) by active pinocytosis, 3) through a gap between endothelial cells due to inflammation,[15,16] and 4) through tight junctions. Immersion fixation, which we applied in the present study, did not sufficiently preserve endothelial cells. Since endothelial cells were diffusely stained with reaction product, it is difficult in most cases to identify labeled pinocytotic vesicles, fenestrae, and tight junctions. Therefore, those possible pathways could not be adequately evaluated. In order to identify those structures, systemic vascular

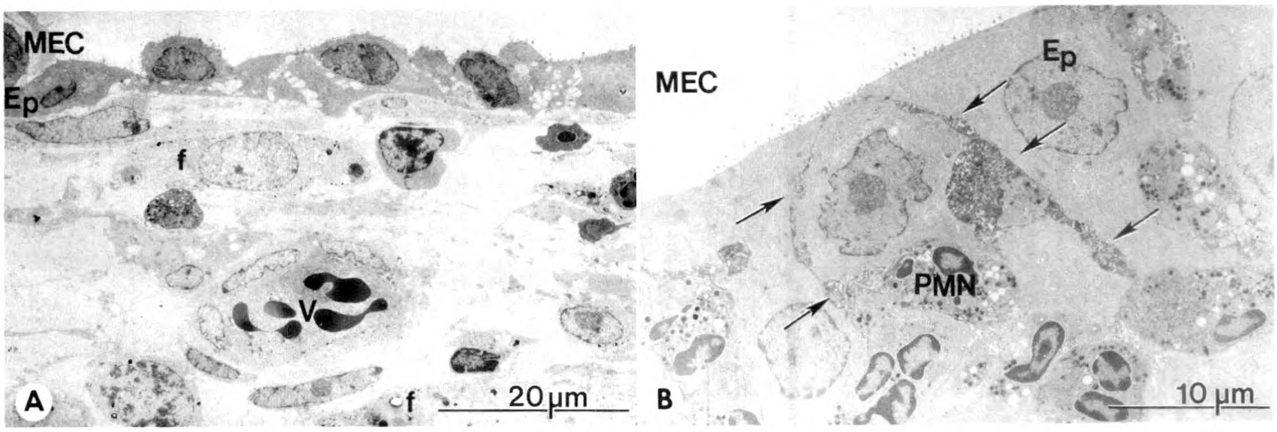

Fig 4. Electron micrographs of middle ear mucosa. MEC — middle ear cavity, Ep — epithelial cell. A) Serous otitis media, 1 week after eustachian tube obstruction. Epithelial cells are cuboidal. Horseradish peroxidase is found in vessel lumen (V) only, not outside it. There is proliferation of fibrocytes (f) in wide subepithelial space, which shows endogenous peroxidase activity. B) Purulent otitis media, 1 week after inoculation. Epithelium shows metaplasia of cuboidal cells. Many polymorphonuclear neutrophils (PMN) are found. Large amount of horseradish peroxidase is detected in intercellular spaces between epithelial cells and in subepithelial space (arrows).

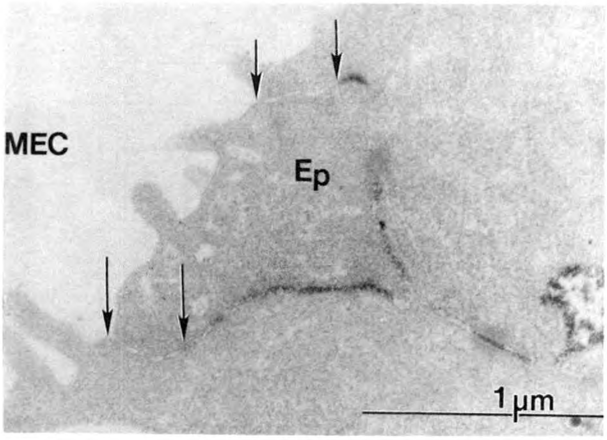

Fig 5. Higher magnification of epithelial cells (Ep) facing middle ear cavity (MEC) 1 week after inoculation. Tight junctions (between arrows) do not contain reaction product.

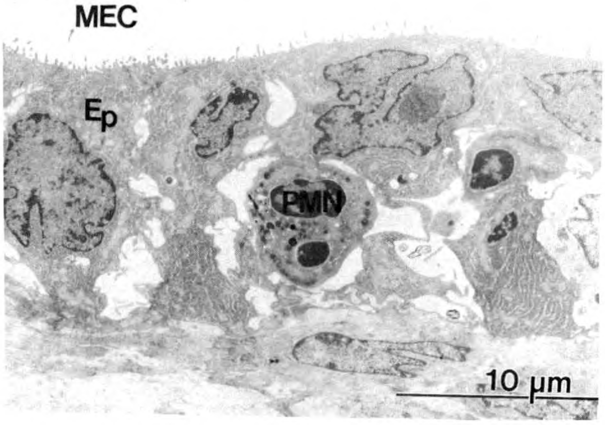

Fig 6. Electron micrograph of purulent otitis media 1 week after inoculation without horseradish peroxidase injection. Endogenous peroxidase is not observed in intercellular space. Some endogenous reaction product is found in polymorphonuclear neutrophil (PMN). MEC — middle ear cavity, Ep — epithelial cell.

perfusion that preserves endothelial cells might be necessary.

Morphologic study did not show HRP (molecular weight, 40,000) in the middle ear cavity, while biochemical study demonstrated both albumin (molecular weight, 70,000) and α2-M (molecular weight, 820,000) in the MEE. This discrepancy has not yet been explained, but two possibilities come to mind. First, HRP circulation time (10 minutes) might have been too short for leakage of protein molecules into the middle ear cavity. If the circulation time was longer, HRP might be absorbed by epithelium and transported to the middle ear cavity. Second, HRP may have existed free in the middle ear cavity and been washed away during processing.

Special attention has been paid to epithelial tight junctions. Some investigators administered HRP into the middle ear cavity of normal guinea pigs and examined the permeability of tight junctions of the middle ear mucosa facing the middle ear cavity to HRP. Haye[17] reported that HRP injected into the middle ear cavity went through epithelial tight junctions. Lim and Hussl[18] reported that HRP was transported into the subepithelial tissue by pinocytosis and that the passage through tight junctions might not have taken place. In the present study, we administered HRP into the bloodstream and examined the passage of HRP from the subepithelial tissue, where blood vessels were located, to the middle ear cavity. The results showed that epithelial tight junctions facing the middle ear cavity prevented HRP from going through the intercellular cleft to the middle ear cavity in the POM animals. These findings suggest that the tight junctions between epithelial cells in the middle ear mucosa can act as barriers to macromolecular substances during POM. However, this barrier may be permeable to smaller molecular substances, since many therapeutic agents can be transported into the middle ear cavity after systemic injection.

It is generally believed that albumin and α2-M in MEE are proteins derived from plasma through vascular leakage. They are biochemical markers of vascular permeability.[1,2,4] The concentration ratio of MEE to plasma was much higher in POM than in SOM. This finding was consistent with that of a previous study.[19] Furthermore, other biochemical parameters such as numbers of neutrophils and levels of lysozome[20] and prostaglandins[21] were also reported to be significantly higher in POM than in SOM. These biochemical findings suggested that the activity of chemical mediators was higher in POM than in SOM, and that these mediators might be responsible for the increased vascular permeability in the middle ear mucosa.

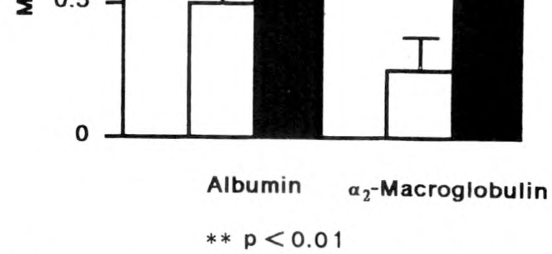

Fig 7. Concentration ratios of middle ear effusion (MEE) to plasma of albumin and α2-macroglobulin at 1 week. Both MEE/plasma ratios were much higher in purulent otitis media (POM) than in serous otitis media (SOM).

We have tried to explore the possibility of utilizing the biochemical findings of MEE in the evaluation of the clinical course of the otitis media. This HRP study supported the notion that biochemical findings of MEE reflect the degree of inflammatory changes in different stages of the otitis media.

It is concluded that a higher level of HRP leakage from vessels was observed in POM than in SOM, and that this morphologic finding was substantiated by the biochemical findings in MEEs evaluated for levels of $\alpha 2$-M and albumin.

ACKNOWLEDGMENT — We are grateful for the excellent technical assistance of Karen Robinson.

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CHANGES IN THE CAPILLARIES OF THE STRIA VASCULARIS AFTER HEMORRHAGIC SHOCK

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As a result of severe hemorrhagic shock in guinea pigs, the blood flow in the capillaries of the stria vascularis was blocked, but that of the spiral ligament was unaffected. It is therefore postulated that the thick layer of basal cells and fibrocytes around the stria vascularis and the capillaries leaving the stria vascularis plays an important role in the formation of blood sludging.

KEY WORDS — blood sludging, hemorrhagic shock, horseradish peroxidase, stria vascularis.

INTRODUCTION

In a previous study, when guinea pigs were killed by decapitation, blood sludging appeared only in the capillaries of the stria vascularis.[1] Blood sludging was not observed when the cochleas were fixed with glutaraldehyde before decapitation. However, blood sludging was present in the capillaries of the stria vascularis when fixation was performed after decapitation.[1] We speculated that blood sludging was induced by acute anoxia or hypotension; however, decapitation is not a good method for investigating this hypothesis. A better experiment was designed to use in vivo fixation. In the present study we induced an anoxic situation through hemorrhage. If the above hypothesis is correct, blood sludging should occur only in the capillaries of the stria vascularis after the hemorrhagic shock. In clinical practice, patients sometimes complain of hearing loss after experiencing hemorrhagic shock. This experiment may provide insight into the cause of this hearing loss.

MATERIALS AND METHODS

Eight guinea pigs weighing 350 g were anesthetized with pentobarbital (30 mg/kg intraperitoneally). The femoral artery was operatively exposed and cannulated under an operating microscope. A catheter was inserted into the femoral artery and connected to a pressure transducer (T-12AD, Gould). An electrocardiogram was recorded with use of a limb lead. This arrangement made it possible to measure simultaneously the arterial blood pressure and the heartbeat rhythm of the guinea pig. The tympanic bulla on the left side was exposed and opened. A catheter was then inserted into the right common carotid artery with its tip in the aortic arch.

In three animals (group A), about half of the circulating blood (from 11 to 14 mL) was removed over 3 minutes through the catheter. After blood loss, hemorrhagic shock occurred. Arterial blood pressure promptly decreased to nearly 0 mm Hg within 3 minutes, and the heart rate also decreased to almost half of its initial rate (Fig 1). Seven minutes after hemorrhagic shock, when the heart rate was 66 beats per minute, 45 mg/kg of horseradish peroxidase (HRP) (Sigma, Type VI) dissolved in 1 mL of water was injected through the catheter into the right common carotid artery.

In two animals (group B), 3 mL of circulating blood was removed within 1 minute. Arterial blood pressure decreased to about 20 mm Hg. Thereafter the circulating blood was periodically removed in order to keep blood pressure at 20 mm Hg. Eight minutes after blood removal was initiated (by which time a total of 8 to 9 mL of circulating blood had been removed), HRP was injected through the catheter into the right common carotid artery (Fig 2).

One minute after the HRP injection, the left cochleas of both groups A and B were infused with a fixing solution of 2% glutaraldehyde buffered with 0.1 mol/L cacodylate. Five minutes after infusion of the fixative, the animals were decapitated. The left cochleas were subsequently microdissected to separate the stria vascularis. These samples were further fixed for 1 hour with 2% glutaraldehyde and then washed three times with 0.1 mol/L cacodylate buffer (containing 8% sucrose, pH 7.2). They were then incubated for 1 hour at room temperature by a

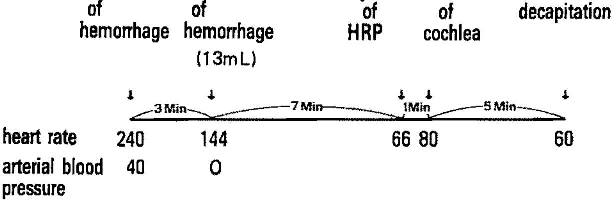

Fig 1. Protocol for group A animals. Thirteen milliliters of circulating blood was removed.

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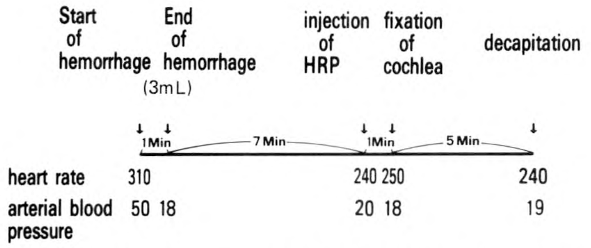

Fig 2. Protocol for group B animals. Three milliliters of circulating blood was removed. After removal of this blood, circulating blood was occasionally removed in order to keep arterial blood pressure at 20 mm Hg.

modification of the Graham-Karnovsky method[2] (0.05 mol/L Tris–hydrochloric acid buffer, pH 7.6, 10 mL containing 0.002% H_2O_2 and 8 mg of 3,3′-diaminobenzidine tetrahydrochloride). They were then washed three times in 0.1 mol/L cacodylate buffer, and then postfixed for 40 minutes in 2% osmium tetroxide, dehydrated, and embedded in Epon 812. Ultrathin radial sections of each turn of the lateral wall of the cochlea were taken at several locations and observed through an electron microscope. The distance between sections was 0.1 to 0.2 mm. One hundred cross-sectioned capillaries of the stria vascularis in every turn were examined and classified into the following five different types.

The classification of capillary types was described in a previous paper.[1] Type 1 capillaries had no blood sludging and no HRP leakage. Type 2 capillaries had no blood sludging and slight HRP leakage. Type 3 capillaries had blood sludging but no HRP leakage. Type 4 capillaries had blood sludging and HRP leakage. Type 5 capillaries had blood sludging, and HRP was not observed in them.

Three animals served as controls (group C). Stria vascularis/spiral ligament samples were taken from the cochlea by the same method described above, but without any removal of blood prior to killing.

RESULTS

In group A, in which about half of the circulating blood was removed, blood sludging was observed in the capillaries of the stria vascularis, and HRP reaction products were not observed. However, HRP reaction products with no blood sludging were found in the capillaries of the spiral ligament (Fig 3). Many marginal folds were observed inside the capillaries of the stria vascularis (Fig 3, arrow). The HRP reaction products in the capillaries entering the stria vascularis were condensed and amorphous (Fig 4A). Complete blood sludging was observed in those areas in which the capillaries passed through the basal cell layer and the blood vessels penetrated the stria vascularis for a few microns (Fig 4B). No HRP reaction products were observed in the capillaries after blood sludging appeared. Blood sludging was also observed in those capillaries leaving the stria vascularis, which were tightly surrounded by a layer of basal cells and fibrocytes. No HRP reaction products were observed in these capillaries (Fig 5). Type 5 capillaries were observed in large numbers in every turn of the cochlea except the basal turn (Table 1). In the basal turn, 17% of the capillaries were type 5, and 34.3% of the capillaries with no blood sludging were types 1 and 2.

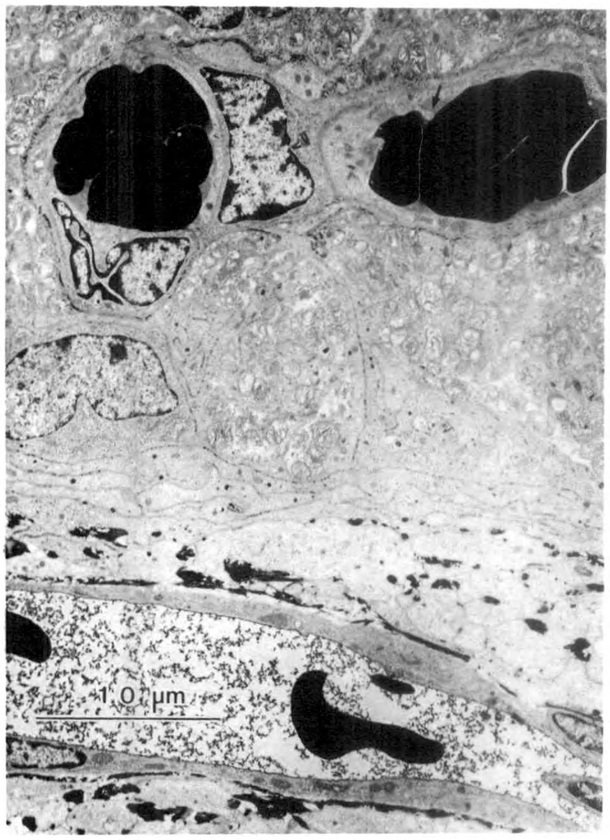

Fig 3. Blood sludging in capillaries of stria vascularis after hemorrhagic shock, and no horseradish peroxidase reaction products in them (type 5 capillary). In capillary of spiral ligament, sparse horseradish peroxidase reaction products and no blood sludging were observed. Arrow — marginal fold.

In group B (the animals whose blood pressure was kept to 20 mm Hg), blood sludging was absent in almost all the capillaries of the stria vascularis in every turn of the cochlea (Table 2). Leakage of HRP without blood sludging (type 2 capillaries, Table 2) was observed in about half of the capillaries. In group C (control group), the percentage of capillaries without blood sludging (types 1 and 2) was the same as in group B, although the percentage of type 2 capillaries was lower than in group B (Table 3). Sparse HRP reaction products were observed in the capillaries of the stria vascularis (Fig 6).

DISCUSSION

In previous papers[1,3] it was reported that blood sludging appeared in the stria vascularis following decapitation. It was speculated that the layer of basal cells and fibrocytes surrounding the capil-

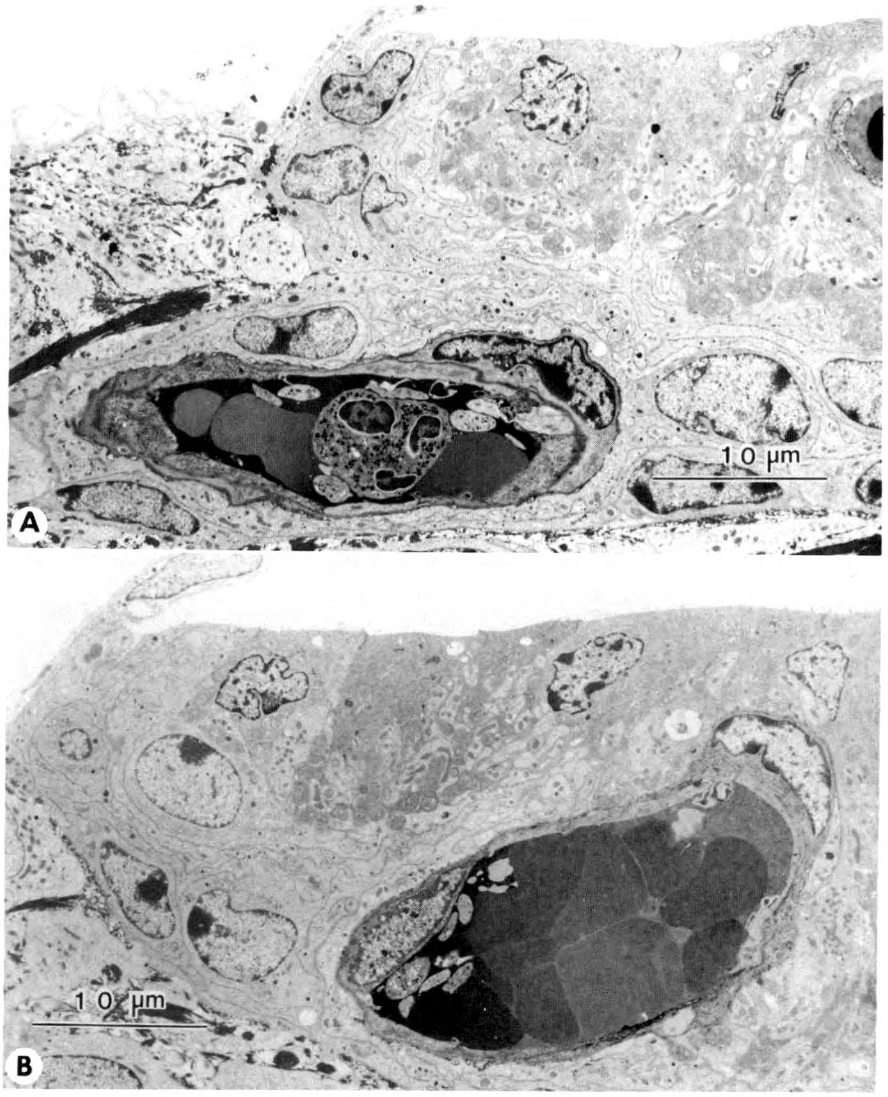

Fig 4. A) Capillary just entering stria vascularis. Horseradish peroxidase reaction products were present in plasma space. B) Capillary of A has penetrated into stria vascularis. Although horseradish peroxidase reaction products were observed in capillary near basal cell layer, they were not observed within few microns from basal cell layer, where blood sludging was complete.

laries leaving the stria vascularis contracted as a result of acute anoxia or hypotension and that blood sludging was thus induced. In the present experiment it was further shown that blood sludging was also induced through hemorrhagic shock, but only in the capillaries of the stria vascularis. It is evident that blood flow in the labyrinthine artery and the capillaries of the spiral ligament was maintained despite hemorrhagic shock, since HRP reaction products were observed in the capillaries of the spiral ligament. It has been demonstrated elsewhere that blood sludging and stasis are observed in the pial vessels of cats at arterial pressures below 20 mm Hg,[4] although a moderate fall in systemic blood pressure results immediately in dilatation of the small pial arteries.[5,6] Therefore, it is not surprising that blood sludging was observed in the capillaries of the stria vascularis after severe hemorrhagic shock. The presence of type 5 capillaries means that a complete blockage of blood flow occurred before the HRP injection. The presence of type 3 and type 4 capillaries means that blood sludging cannot completely block the blood flow of the stria vascularis. When arterial blood pressure was kept at about half of its initial level, blood sludging was not observed in the capillaries of the stria vascularis, although capillary permeability slightly increased (Table 2). Sakagami et al[7] reported that the capillary permeability was enhanced under acute hypotension only in the capillaries of the stria vascularis but not of the spiral ligament. In their paper, the arterial blood pressure was decreased to about half of its initial level, as it was in our present experiment in group B. It is believed that increased capillary permeability precedes the blood sludging in acute hypotension.

It is interesting to note that only the strial blood flow was blocked, while the blood flow in the vessels of the spiral ligament was maintained. If the endolymph is produced from the capillaries of the stria vascularis, and the maintenance of the resting endocochlear potential resides with the stria vascularis, the maintenance of the blood flow in the stria vascularis should be more important than that in the spiral ligament. Fog[5,8] was the first to report

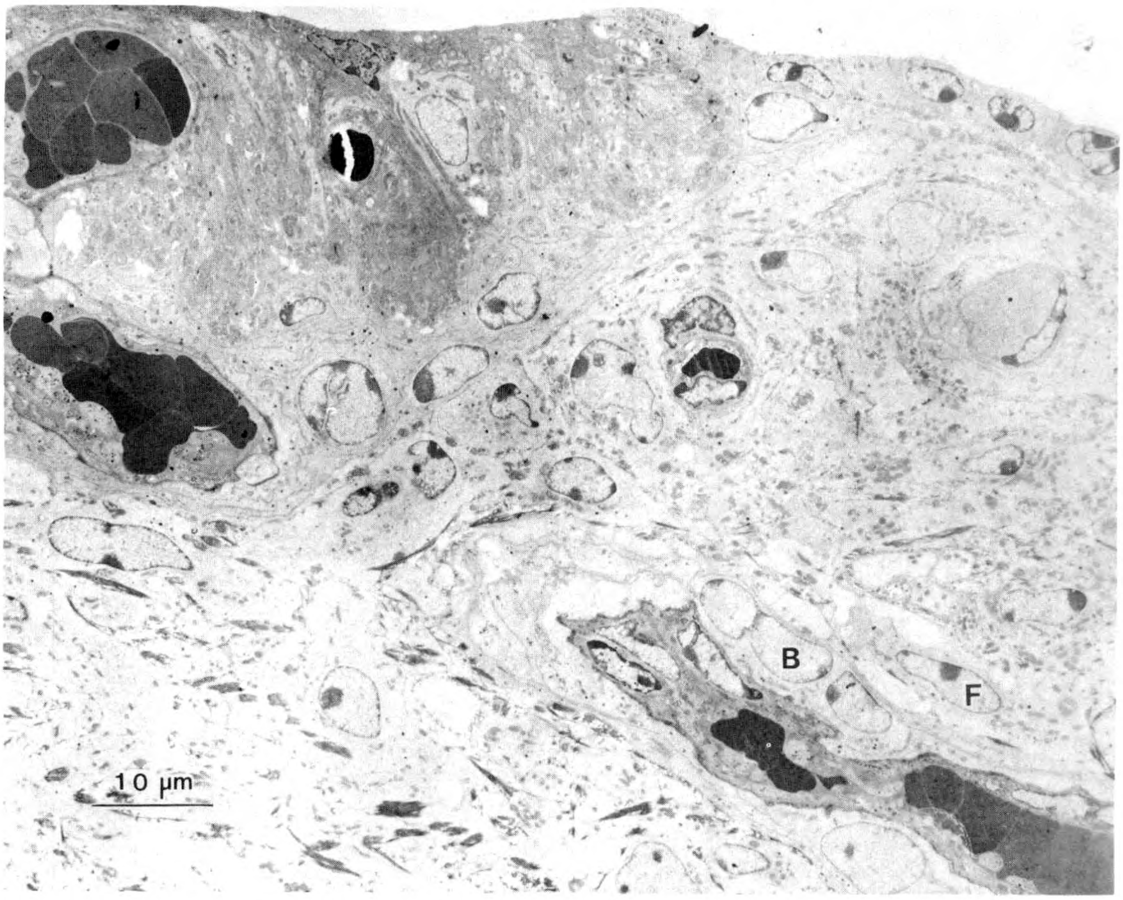

Fig 5. Thick layer of basal cells and fibrocytes surrounding capillary leaving stria vascularis. Blood sludging and no horseradish peroxidase reaction products were observed. B — basal cell, F — fibrocyte.

cerebral autoregulation in terms of blood flow constancy during perfusion blood pressure changes. It was recently reported that the autoregulatory response of blood vessels in the brain is not uniform with regard to region, vessel size, and rate of perfusion pressure change.[9] It was reported that a reduction in arterial pressure through hemorrhage produced a significantly greater decrease in blood flow in the cerebrum than in the brain stem. In any case,

TABLE 1. PERCENTAGE OF FIVE TYPES OF STRIAL CAPILLARIES IN COCHLEA AFTER REMOVAL OF ABOUT HALF OF CIRCULATING BLOOD (GROUP A)

Turn	*Animal*	*Type 1* (%)	*Type 2* (%)	*Type 3* (%)	*Type 4* (%)	*Type 5* (%)
Basal	1	6	26	20	28	20
	2	6	30	27	23	14
	3	6	29	23	25	17
	Mean	6.0	28.3	23.3	25.3	
		34.3		48.7		17.0
Second	1	0	0	0	0	100
	2	0	9	7	9	75
	3	0	4	3	4	89
	Mean	0	4.3	3.3	4.3	
		4.3		7.7		88
Third	1	5	0	0	0	95
	2	6	0	9	9	76
	3	4	0	4	4	88
	Mean	5.0	0	4.3	4.3	
		5.0		8.7		86.3
Fourth	1	0	0	0	0	100
	2	0	0	0	0	100
	3	0	0	0	0	100
	Mean	0	0	0	0	
		0		0		100

TABLE 2. PERCENTAGE OF FIVE TYPES OF STRIAL CAPILLARIES IN COCHLEA AFTER REMOVAL OF 3 ML OF CIRCULATING BLOOD AND KEEPING ARTERIAL BLOOD PRESSURE AT 20 MM HG (GROUP B)

Turn	*Animal*	*Type 1* (%)	*Type 2* (%)	*Type 3* (%)	*Type 4* (%)	*Type 5* (%)
Basal	1	68	28	3	1	0
	2	47	52	0	0	1
	Mean	57.5	40	1.5	0.5	
		97.5		2.0		0.5
Second	1	63	35	2	0	0
	2	44	54	2	0	0
	Mean	53.5	44.5	2	0	
		98.0		2.0		0
Third	1	72	26	2	0	0
	2	34	57	3	6	0
	Mean	53.0	41.5	2.5	3	0
		94.5		5.5		0
Fourth	1	61	39	0	0	0
	2	40	53	7	0	0
	Mean	50.5	46.0	3.5	0	
		96.5		3.5		0

TABLE 3. PERCENTAGE OF FIVE TYPES OF STRIAL CAPILLARIES IN COCHLEA WITHOUT REMOVAL OF CIRCULATING BLOOD (CONTROL GROUP C)

Turn	*Animal*	*Type 1* (%)	*Type 2* (%)	*Type 3* (%)	*Type 4* (%)	*Type 5* (%)
Basal	1	71	27	1	1	0
	2	96	4	0	0	0
	3	78	22	0	0	0
	Mean	81.7	17.7	0.3	0.3	
		99.4		0.6		0
Second	1	69	29	0	2	0
	2	97	3	0	0	0
	3	59	41	0	0	0
	Mean	75.0	24.3	0	0.7	
		99.3		0.7		0
Third	1	72	25	1	2	0
	2	95	5	0	0	0
	3	63	31	0	6	0
	Mean	76.7	20.3	0.3	2.7	
		97.0		3.0		0
Fourth	1	71	28	0	1	0
	2	92	8	0	0	0
	3	70	25	2	3	0
	Mean	77.7	20.3	0.7	1.3	
		98		2		0

the blood flow is always maintained in the more important regions through autoregulation. We still cannot explain why blood sludging appeared in the capillaries of the stria vascularis and not in those of the spiral ligament. The vessels of the stria vascularis and the spiral ligament are both supplied from the same arteries (radiating arteries) and unite in the same venules (collecting venules).[10] The obvious difference between them is the thick layer of basal cells and fibrocytes around the stria vascularis and around the capillaries leaving the stria vascularis.[3] It is therefore thought that this layer plays an important role when blood sludging occurs.

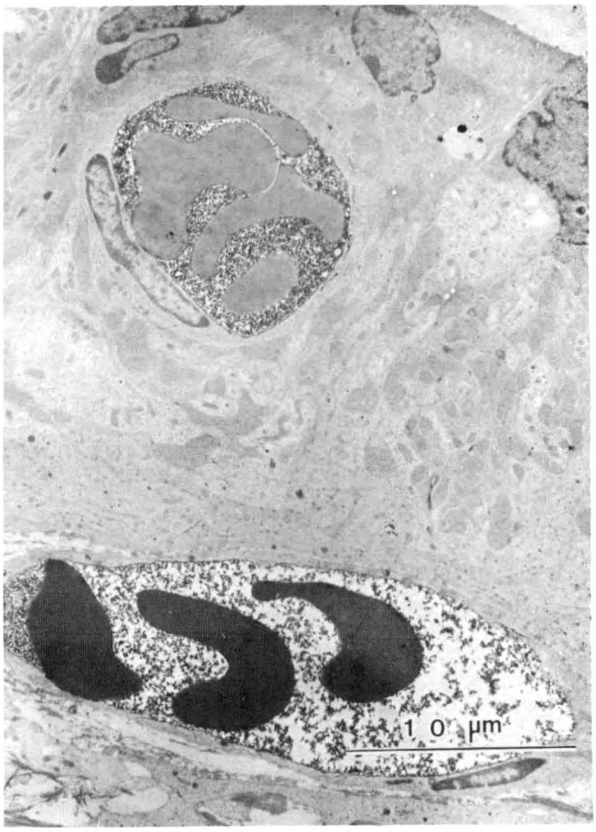

Fig 6. Lateral wall of cochlea of control animal. Cochlea was fixed 5 minutes before decapitation. Sparse horseradish peroxidase reaction products and no blood sludging were observed in both capillaries of stria vascularis and spiral ligament.

After hemorrhagic shock was induced through the removal of a large amount of the circulating volume of blood, blood sludging appeared in almost all the capillaries of the stria vascularis, but the percentage of type 5 capillaries was lower in the basal turn than in the upper turns. This discrepancy may be due to differences in the feeding arteries. While the basal turn is fed mainly by the vestibulocochlear artery, the upper turns are fed by the common cochlear artery.[11] Another reason may be that the number of capillaries entering the stria vascularis, leaving it, and passing through the spiral ligament differs between the basal turn and the upper turns.[12] In the basal turn the capillaries enter the stria vascularis at a higher rate than they leave it, while in the upper turns they enter it at a lower rate than they leave it.

SUMMARY

As a result of severe hemorrhagic shock in guinea pigs, capillaries that had blood sludging were observed throughout the stria vascularis, although they were far less frequent in the basal turn than in the upper turns. Even after severe hemorrhagic shock, the tracer (HRP) intravenously injected was observed in the capillaries of the spiral ligament without blood sludging. We therefore postulate that the thick layer of basal cells and fibrocytes around the stria vascularis and the capillaries leaving the stria vascularis play an important causative role in blood sludging.

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Ann Otol Rhinol Laryngol 99:1990

HISTAMINE STIMULATION OF MUCOCILIARY ACTIVITY IN THE RABBIT MAXILLARY SINUS

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The in vivo effect of histamine on mucociliary activity in the rabbit maxillary sinus was investigated by injecting histamine into the maxillary artery and recording the responses with a photoelectric technique. Histamine stimulated the mucociliary activity dose-dependently in the dose range 10 to 1,000 μg/kg. The maximum response was 31.6% ±3.7% at a dose of 50 μg/kg. The histamine-induced stimulation of the mucociliary activity was characterized by a short latency with a peak response within 1 to 2 minutes and a slow decline lasting about 5 minutes. The response displayed tachyphylaxis. Cholinergic blockade with atropine did not affect the response to histamine. Blockade of H1 receptors with pyrilamine abolished the response to histamine, whereas blockade of H2 receptors with cimetidine was without effect. The H2 agonist dimaprit failed to stimulate the mucociliary activity. It is concluded that histamine stimulates the mucociliary activity in the rabbit maxillary sinus via H1 receptors.

KEY WORDS — histamine, mucociliary activity.

INTRODUCTION

The mucociliary system of the respiratory mucosa represents the first line of defense in the airways. This important defense mechanism may malfunction in various pathologic conditions of the respiratory tract. For example, impairment of the mucociliary function in the lower airways has been reported in patients with asthma or chronic bronchitis,[1,2] while a similar mucociliary dysfunction has been found in the upper airways in patients with chronic sinusitis.[3] This impairment can be related to the liberation of inflammatory mediators,[2,4] although it has not been possible to identify the role played by each one individually. One of the putative mediators, histamine, has been studied in various experimental models, but its effect on the mucociliary function is still obscure.

Many in vitro studies have failed to demonstrate an effect of histamine on ciliary activity.[5,6] Contrary to these reports, Wanner et al[7] found that histamine produced modest stimulation of ciliary beat frequency in isolated tracheal cells from ewes, but only in relatively high doses.

Histamine is released in response to inflammatory and allergic reactions,[8] both of which occur frequently in the upper airways. However, the effect of histamine has not been studied hitherto on the mucociliary activity in the upper airways. The results obtained from the lower airways are conflicting, and it is doubtful if they can be extrapolated to the upper airways. It is therefore of interest to elucidate the effects of histamine by use of an experimental animal model allowing in vivo study of the mucociliary activity in the upper airways. The present study reports the in vivo effect on the mucociliary activity in the rabbit maxillary sinus of intra-arterial administration of histamine and its relation to H1, H2, and muscarinic receptors.

METHODS

The experiments were performed on rabbits of both sexes weighing 1.8 to 3.0 kg. Details of anesthetic and operative techniques have been published previously.[9] The animals were anesthetized with intramuscular urethane 2.0 g/kg as an initial dose, followed by 0.5 g/kg intravenously during the beginning of the operation. The arterial inlet for the test substances was a retrograde cannula in the facial or lingual artery, continuously perfused with saline at 2 mL/h. The mucosa in the maxillary sinus was exposed through a trephination hole of about 2 x 8 mm that was covered immediately with an antimist window. The slit between the window and the bone was sealed with bone wax (Ethicon) in order to avoid desiccation of the mucous membrane.

The mucociliary activity (visible as flickering light reflections) was observed through a binocular microscope, and the transportation of small particles like mucus clumps and shed cells was the criterion for a working preparation. One of the eyepieces then was switched to a phototransducer, and the mucociliary activity was recorded by a photoelectric technique. The mucociliary wave pattern was monitored continuously on an oscilloscope and recorded on an ink writer during challenges. The recordings were analyzed by a computerized frequency calculator, the mucociliary wave frequency being expressed in waves per minute and calculated every 10 seconds during challenges and at intervals

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of 1 minute otherwise. The induced frequency changes were expressed as percentages of the mucociliary wave frequency (frequency zero level) at the time of the administration of the tested substances. The dose-response and time-course curves were plotted from the maximum mucociliary wave frequency change during the first 5 minutes after each challenge. Electrocardiographic activity and rectal temperature were monitored. Body temperature was maintained at 37°C to 38.5°C by a heating pad. Respiration was sensed by a Hewlett Packard Toccotransducer 15278 B placed on the thorax and was recorded simultaneously with the mucociliary activity.

The following drugs were used: histamine dihydrochloride (Sigma, USA), pyrilamine maleate (mepyramine; Sigma, USA), cimetidine (Tagamet; SK&F, Belgium), and atropine sulfate (ACO, Sweden). Dimaprit (dimethylamino-propyl-isothiourea) was a generous gift from Dr J. Skidmore, SK&F Research Ltd, England. Doses are expressed as concentrations of the respective salt. All substances were dissolved in saline.

The intra-arterial route for administration of histamine was chosen for the following reasons. Although topical administration of histamine minimizes general side effects and mimics the release of histamine from mucosal mast cells, this method of application carries some disadvantages for mucociliary studies. Local administration causes tactile stimulation that increases the ciliary beat frequency.[10] The rheologic properties of mucus are influenced by the applied solution, and this in turn could interfere with the mucociliary activity. Moreover, intra-arterial histamine has been used in other studies of airway physiology.[11]

Experimental Procedure. Histamine was given as a bolus injection of 0.2 mL in all experiments.

1. The effect of increasing doses of histamine was investigated in 16 rabbits, and a log dose-response curve was plotted in the interval 0.01 to 1,000 µg/kg (corresponding to 54.3 pmol/kg to 5.43 µmol/kg histamine dihydrochloride). The time lapse between challenges was 30 to 60 minutes.

2. In order to investigate if there was any tachyphylaxis to histamine, six rabbits were challenged with three consecutive 50-µg/kg injections of histamine at 1-hour intervals.

3. The effect of a 50-µg/kg histamine dose during cholinergic blockade by atropine was investigated in six rabbits. Atropine was given at a dose of 0.2 mg/kg as an intra-arterial bolus injection of 0.2 mL. The rabbits were challenged with histamine 2 minutes after the atropine injection.

4. The effect of histamine at 50 µg/kg during H1 receptor blockade by pyrilamine was investigated in six rabbits. Pyrilamine (mepyramine) 4 mg/kg was given as an intravenous infusion of 1 mL over 1 minute. The rabbits were challenged with histamine 10 to 15 minutes after the pyrilamine infusion.

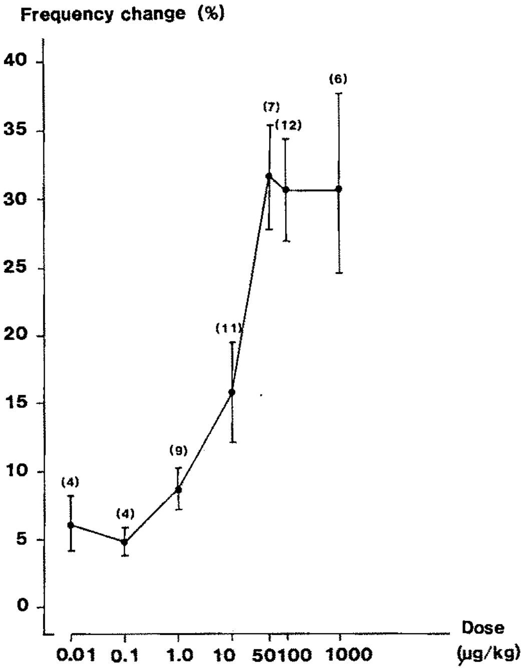

Fig 1. Effect of histamine on mucociliary activity in dose range 0.01 to 1,000 µg/kg (corresponding to 54.3 pmol/kg to 5.43 µmol/kg). Figures in parentheses refer to number of experiments performed at each dose. Results are expressed as means ± SEM. The correlation coefficient for raw data was r = 0.66 (n = 16). Frequency zero level was 1,234 ± 21 waves/min.

5. The effect of histamine at 50 µg/kg during H2 receptor blockade by cimetidine was investigated in six rabbits. Cimetidine at 5 mg/kg was given as an intravenous infusion of 1 mL over 1 minute. The rabbits were challenged with histamine 10 to 15 minutes after the cimetidine infusion.

6. Five rabbits were challenged with the H2 receptor agonist dimaprit at 10, 50, and 250 µg/kg given as bolus doses of 0.2 mL. The time lapse between challenges was 20 to 30 minutes.

Six rabbits received histamine (50 µg/kg) only, as a control.

The doses of the antagonists and the time intervals between the antagonists and the subsequent injections of histamine were chosen in accordance with results of previous investigations using the same experimental model[12] and in vivo experiments performed by other research groups.[13-15]

The results are expressed as means and standard error of the mean (SEM). The maximum response and the area under the curve were subjected to a parametric *t* test, except for the experiments with cimetidine, in which the Mann-Whitney U test was used. Only p values smaller than .05 were considered significant.

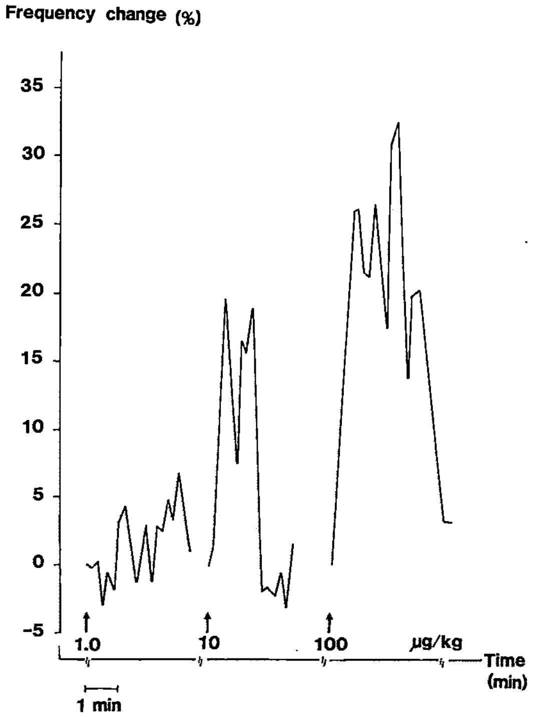

Fig 2. Effect of histamine on mucociliary activity in one rabbit in doses 1.0, 10, and 100 μg/kg. Results are expressed as percentages of basal mucociliary level. Frequency zero levels were 1,083, 1,077, and 970, respectively.

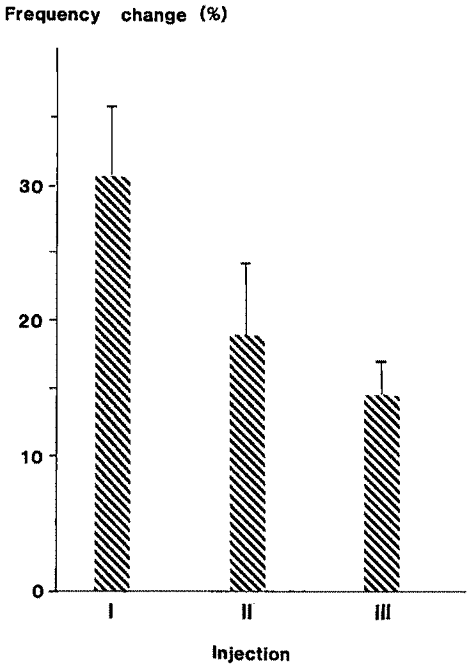

Fig 3. Maximum response of mucociliary activity after three consecutive injections of histamine at dose of 50 μg/kg at intervals of 1 hour. Two-way analysis of variance revealed significant difference between three injections ($p < .05$). Linear regression of raw data displayed slope of −8.0 and correlation coefficient of $r = 0.55$.

RESULTS

Injections of saline, used to dissolve all the tested substances, did not influence the mucociliary activity.

Histamine stimulated the mucociliary activity dose-dependently in the dose interval 10 to 1,000 μg/kg (corresponding to 54.3 nmol/kg to 5.43 μmol/kg); the maximum response was 31.6% ± 3.7% for a dose of 50 μg/kg. The dose-response relationship is illustrated in Fig 1, which summarizes the results obtained from 53 experiments in 16 rabbits.

The histamine-induced stimulation of the mucociliary activity is characterized by a short latency with a peak response within 1 to 2 minutes and a slow decline of about 5 minutes. The higher the dose given, the longer the duration of the effect. Figure 2 shows the results from one rabbit challenged with three consecutive but different doses of histamine in ascending order.

In six rabbits challenged with three consecutive injections of histamine at a dose of 50 μg/kg, tachyphylaxis was found (Fig 3).

Cholinergic blockade by atropine (0.2 mg/kg intra-arterially) did not affect the stimulating effect of histamine on the mucociliary activity (Fig 4A). The maximum response ($p > .5$) and the areas under the curves ($p > .5$) were not significantly different from those of the control experiments. It is also evident from Fig 4A that the time-course of the response with or without atropine was almost identical.

Pretreatment with the H1 receptor antagonist pyrilamine (4 mg/kg intravenously) abolished the response to histamine (Fig 4B). Both the maximum responses ($p < .001$) and the area under the curve ($p < .05$) were reduced significantly.

Pretreatment with the H2 receptor antagonist cimetidine (5 mg/kg intravenously) did not affect the response to histamine (Fig 4C). There is no statistically significant difference between the results obtained with and without cimetidine, neither for maximum responses ($p = .067$) nor for the area under the curve ($p = .41$).

The H2 receptor agonist dimaprit failed to stimulate the mucociliary activity at the doses of 10, 50, and 250 μg/kg. Maximum responses and the area under the curve did not differ statistically from those of saline control experiments.

The H1 receptor antagonist pyrilamine stimulated the mucociliary activity per se, whereas the H2 receptor antagonists cimetidine and atropine were without effect. The pyrilamine-induced stimulation was characterized by a longer latency than that for histamine, no stimulation of the mucociliary activity occurring during the first minute. The maximum response, 18.5% ± 2.5% ($n = 6$), was noted after more than 2 minutes. The duration of the response was less than 10 minutes, and the baseline level was regained before the challenge

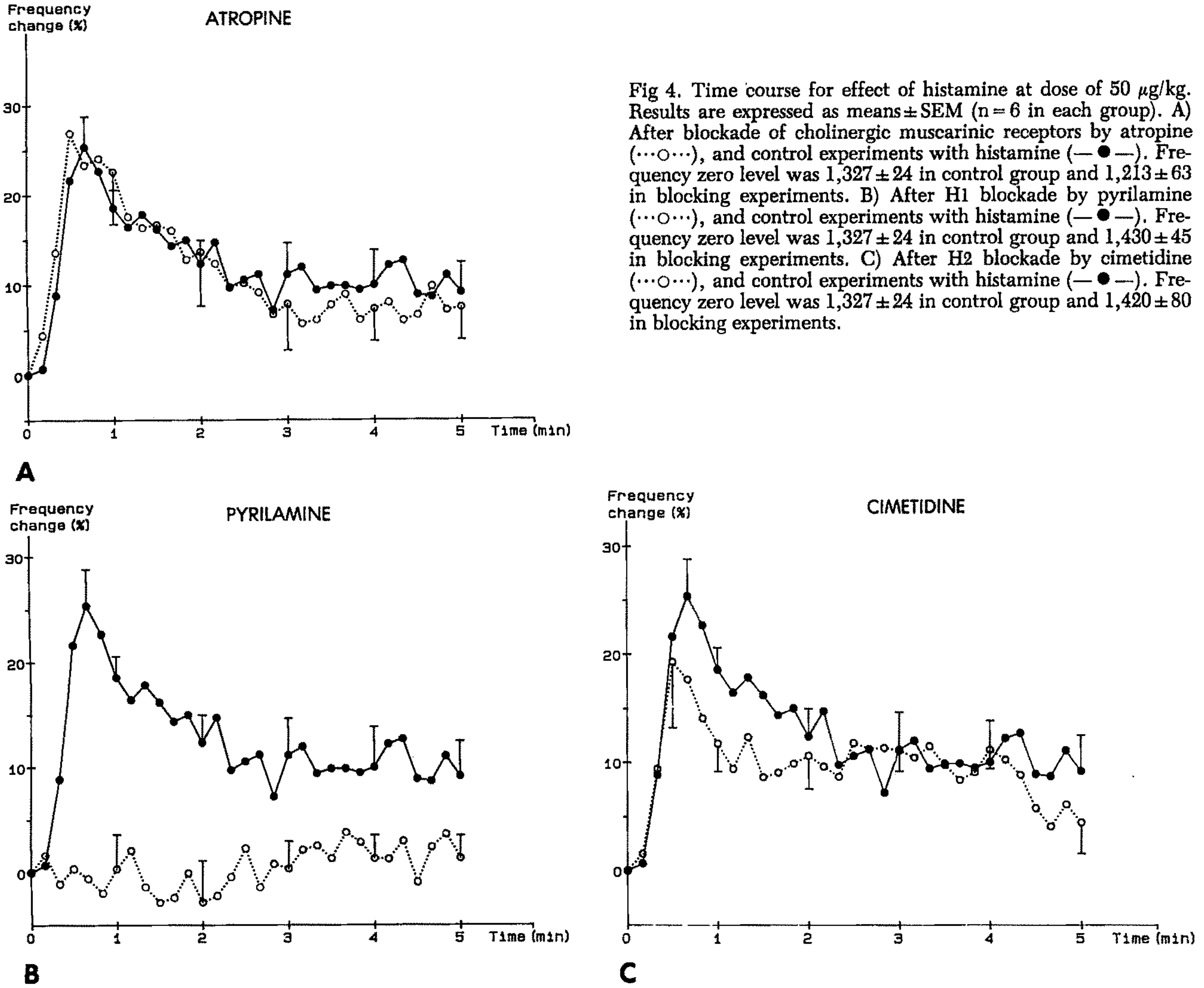

Fig 4. Time course for effect of histamine at dose of 50 μg/kg. Results are expressed as means±SEM (n=6 in each group). A) After blockade of cholinergic muscarinic receptors by atropine (···o···), and control experiments with histamine (—●—). Frequency zero level was 1,327±24 in control group and 1,213±63 in blocking experiments. B) After H1 blockade by pyrilamine (···o···), and control experiments with histamine (—●—). Frequency zero level was 1,327±24 in control group and 1,430±45 in blocking experiments. C) After H2 blockade by cimetidine (···o···), and control experiments with histamine (—●—). Frequency zero level was 1,327±24 in control group and 1,420±80 in blocking experiments.

with histamine. The frequency zero level was 1,344 ±51 before the pyrilamine infusion and 1,430±45 before the subsequent histamine challenge (p=.23, n=6).

Adverse respiratory effects were seen at the highest doses of histamine, probably reflecting its bronchoconstrictor action. These effects were characterized by a tachypnea starting 18 to 30 seconds after the injection. Two of six rabbits died of apnea preceded by a short period of tachypnea when given a dose of 1,000 μg/kg. The respiratory effects of histamine were blocked by pyrilamine, whereas pretreatment with atropine or cimetidine had no effect. Pyrilamine per se induced a transient tachypnea in four of six rabbits.

DISCUSSION

Earlier reports concerning the effects of histamine on the mucociliary system have been contradictory. Older in vitro studies failed to demonstrate any effect of histamine on mucociliary function,[5,6] whereas Wanner et al,[7] using an in vitro technique on epithelial cells from the trachea of sheep, reported that histamine had a modest stimulatory effect on the ciliary beat frequency in relatively high concentrations. Contrary to these results, the present investigation shows that histamine has a distinct accelerating effect on mucociliary activity, and that there is a clear dose-response relationship (Figs 1 and 2). A possible explanation for these conflicting results is that the earlier methods were semiquantitative and mainly recorded the occurrence of ciliostasis on in vitro preparations. It is also possible that histamine exerts its effect indirectly via mediators or via neurogenic mechanisms demonstrable only in intact animals.[15]

A detrimental influence on mucociliary function probably triggered by released inflammatory mediators, including histamine, has been described by Chevance,[16] who found that local application of horse serum or pollen in the nose of sensitized rabbits and guinea pigs produced transient stimulation of ciliary activity followed by a decrease or a cessation of ciliary motility. A similar influence has been reported by Iravani and Melville,[17] who in an in vitro investigation of a preparation from the bronchial tree of rats found ciliary incoordination after the administration of high concentrations of histamine. However, no such effect of histamine could be verified in the present investigation, in which supraphysiologic doses like 1,000 μg/kg, while certainly having adverse effects on the respiratory function, still accelerated the mucociliary activity.

"Classic" antihistamines, ie, H1 receptor antagonists, possess additional pharmacologic properties such as anticholinergic and local anesthetic effects.[18] H1 receptor antagonists per se have been reported to depress ciliary motility in vitro.[6,19] However, in the present model, methacholine, a cholinergic receptor agonist, still stimulated the mucociliary activity after blockade by pyrilamine (Dolata, unpublished observations), thereby excluding the possibility that pyrilamine exerts its effect through an unspecific mechanism. The effect of histamine was not affected by atropine (Fig 4A), thus excluding a cholinergic pathway for the histamine-evoked mucociliary acceleration.

Pyrilamine per se stimulated mucociliary activity slightly and elicited a transient tachypnea in four of six rabbits. An analogous situation has been described by Bradley and Russell,[20] who reported that pyrilamine contracted smooth muscle strips from the lower airways but also blocked the histamine-induced contractions of the smooth muscles in the same experimental model, indicating that pyrilamine may possess not only an antagonistic effect on H1 receptors but also an agonistic effect (ie, intrinsic activity).

The observation that the histamine-induced effect was blocked by the H1 receptor antagonist pyrilamine indicates the existence of H1 receptors in the upper respiratory epithelium and/or in effector nerves. Secher et al[21] indirectly suggested the existence of H1 receptors in the sensory trigeminal nerve fibers in humans, and by using a radioligand-binding technique Ishibe et al[22] showed the existence of binding sites for H1 receptor ligands in the nasal mucosa in both humans and guinea pigs. If sensory C fibers are involved in the H1-mediated effect on mucociliary activity, this can be elucidated further by pretreatment with capsaicin, a substance that depletes neuropeptides in sensory nerve endings.[23]

The time-course of the histamine response after H2 blockade with cimetidine showed a tendency toward suppression of mucociliary activity compared with that obtained after histamine alone, but there is not a statistically significant difference. However, an H2-mediated effect definitely can be excluded, because rabbits challenged with dimaprit did not increase their mucociliary activity. Dimaprit is a highly specific H2 receptor agonist, having 17% to 70% of the potency of histamine on H2 receptors for similar maximal responses but less than 0.0001% of the activity of histamine on H1 receptors.[24]

The experiments with consecutive injections of histamine at a dose of 50 μg/kg (Fig 3) revealed tachyphylaxis to histamine. Experiments by Bradley and Russell[20] have shown that tachyphylaxis to histamine can be dose-dependent; high concentrations of histamine led to the development of tachyphylaxis with respect to the capability to contract airway smooth muscles, while lower concentrations did not. In the present investigation tachyphylaxis developed with a dose of histamine that induced maximum stimulation of mucociliary activity. Histamine develops tachyphylaxis in the upper airways of humans with respect to tickling, sneezing, and hypersecretion,[21] ie, symptoms mediated by trigeminal sensory nerve fibers. Since stimulation of sensory C fibers in our experimental model enhances mucociliary activity,[25,26] sensory nerve fibers might be involved in the histamine-induced stimulation of mucociliary activity. Experiments using capsaicin are necessary to evaluate this possibility further.

There are reports that histamine via H1 receptors induces net fluxes of Na^+ and Cl^- toward the luminal side of the mucosa.[27] This will affect the water content of both the periciliary fluid and the mucus, thereby interfering with the mucociliary system.[27,28] One may therefore speculate that the accelerating effect of histamine is due to its action on ion fluxes over the respiratory epithelium. The animal model used here does not permit us to investigate whether the apparent stimulation of mucociliary activity by histamine reflects such ion-flux changes.

The bolus doses of histamine used in the present study are high enough to cause changes in systemic blood pressure[14,29] that in turn also will affect the local blood flow in the maxillary sinus. Moreover, in vivo and in vitro studies have indicated the existence of H1 and H2 receptors on nasal blood vessels with a distribution that varies among different species.[21,30,31] It therefore could be hypothesized that the effect of histamine on mucociliary activity is in fact the result of changes in the vascular bed of the ciliated mucous membrane. However, measurement of the blood flow with a laser-Doppler flowmeter showed that a single intra-arterial injection of 100 μg/kg of histamine depressed the local blood flow in the maxillary sinus approximately 90%, the effect lasting 10 to 15 minutes (Dolata, unpublished observations). The same dose of histamine increased mucociliary activity by more than 30% (Fig 1). These results are in accordance with those of Cervin et al,[32] who did not find any correlation between mucociliary activity and local blood flow measured by the laser-Doppler flowmeter.

In conclusion, histamine is capable of stimulating the mucociliary activity in the rabbit maxillary sinus in a dose-dependent fashion. The effect is mediated by H1 receptors and not by H2 or cholinergic muscarinic receptors.

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IMAGING CASE STUDY OF THE MONTH

CHOLESTEROL GRANULOMA PRESENTING IN THE EAR CANAL

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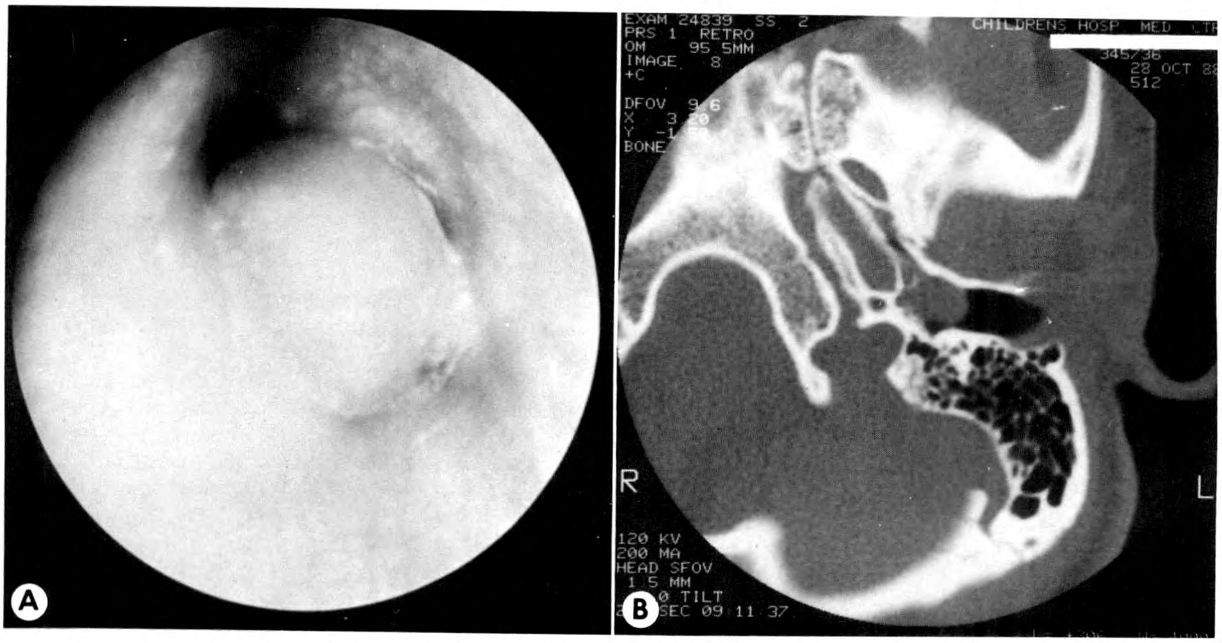
CASE REPORT

A 13-year-old girl was referred for the evaluation of a mass in her left ear. One week prior to evaluation the child had complained of an upper respiratory tract infection associated with otalgia and decreased hearing. Tinnitus, vertigo, and otorrhea were absent. She denied a history of prior otologic problems. On examination, a smooth, blue, compressible, nontender epithelial-covered mass was present in the anterior inferior portion of the left ear canal lateral to the tympanic membrane (see Figure, A). No blood or squamous debris was present in the external auditory canal. The right ear was normal. Her neck had small, nontender, mobile, posterior nodes bilaterally. The remainder of the findings on physical examination were normal. The audiogram showed a mild conductive hearing loss on the left and the tympanogram revealed normal left middle ear pressure with decreased compliance.

A computed tomographic (CT) scan (see Figure, B) showed a round soft-tissue mass that occupied the left hypotympanum, extending into the external auditory canal with punctate elements of calcification in the medial and anteromedial aspects. Questionable thinning or remodeling of bone was present along the medial aspect of the hypotympanum, but there was no disruption of bone between the mass and the jugular bulb or the vertical portion of the left internal carotid artery. The mass did not enhance with contrast. Findings on the scan were otherwise normal.

A left exploratory tympanotomy revealed a mass surrounded by a smooth limiting membrane. This



Cholesterol granuloma. A) Blue mass lateral to tympanic membrane. B) Axial computed tomogram demonstrates soft-tissue density lateral and medial to tympanic membrane. Great vessels have bony covering.

From the Department of Otolaryngology and Maxillofacial Surgery, Division of Pediatric Otolaryngology, University of Cincinnati (Matt, Myer), and the Department of Pediatrics, Children's Hospital Medical Center (Bellet), Cincinnati, Ohio. Dr Matt is currently at the Department of Otolaryngology–Head and Neck Surgery, Indiana University School of Medicine, Indianapolis, Indiana.

REPRINTS — Charles M. Myer III, MD, Division of Pediatric Otolaryngology, Children's Hospital Medical Center, Elland and Bethesda Avenues, Cincinnati, OH 45229-2899.

involved the tympanomeatal flap and extended into the hypotympanum. Polyps were also noted inferior to the eustachian tube orifice. The mass and polyps were removed. The histopathologic examination findings were classic for a cholesterol granuloma: foreign body giant cells and clefts consistent with prior crystals.

DISCUSSION

Cholesterol granuloma is a benign lesion with a typical histologic appearance that may be associated with chronic otitis media. It can occur in any pneumatized bone and can cause expansile changes in surrounding structures. The classic cholesterol granuloma is a blue mass medial to the tympanic membrane. Often a thick middle ear effusion is present.[1-3]

The differential diagnosis includes glomus tumor, hemotympanum, dehiscent or high jugular bulb or carotid artery, implant, osteoma, and encephalocele. These need to be excluded prior to operation. Gentle palpation of the mass is informative and CT scan with enhancement or angiography can delineate vascular structures.[1-3]

Glomus tumors are usually red masses and can cause bulging of the tympanic membrane if large. Pneumo-otoscopy can cause blanching, and pulsations can be observed with a microscope. These tumors enhance with contrast on CT examination.[1-3] A hemotympanum may be difficult to delineate from a cholesterol granuloma, as both can yield a blue-black tympanic membrane. A history of recent trauma or blood dyscrasia may help differentiate the two.[1-3] The dehiscent or high jugular bulb or carotid artery can be identified easily on CT scan. The jugular bulb is often a paler blue and located inferiorly and posteriorly. The carotid is white or pinkish and in the anterior tympanum.[1-3] A Proplast implant can be determined by history and is generally the same deep blue-black as a cholesterol granuloma, but is hard when palpated.[3] Both canal osteomas and exostoses may appear similar to a cholesterol granuloma, but are bone-hard on palpation.[3] Encephaloceles in the ear are generally soft, transparent, and pulsatile. Queckenstedt's test can show enlargement of the mass, and the bony defect is easily identified on CT scan.[3]

Treatment of a cholesterol granuloma can include observation, macroscopic removal, marsupialization, or drainage by tympanostomy tube.[1-3]

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PERILYMPH FISTULA: A COMMON CAUSE OF DIZZINESS AND DYSEQUILIBRIUM?

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Ann Otol Rhinol Laryngol 99:1990

PATHOLOGY CONSULTATION

NON-WARTHIN'S TUMOR ONCOCYTIC LESIONS

R. WARREN J. HARTWICK, MD JOHN G. BATSAKIS, MD

HOUSTON, TEXAS

Oncocytes differ from other epithelial cells of salivary tissues in their excessive proliferation of mitochondria, in turn leading to a hypertrophy and hyperplasia of the chondriome. Oncocytic transformation is not a degenerative process, but rather a redifferentiation of the cells as they attempt to increase their output of high-energy phosphate. As oncocytes divide, their pathologic metabolic activity and mitochondrial phenotype are passed on to their progeny, and these cells produce salivary lesions that range from focal oncocytic metaplasia and hyperplasias to benign and malignant neoplasms — oncocytomas and oncocytic carcinomas.

Table 1 presents the several histopathologic manifestations the mitochondria-rich oncocyte can have in the major salivary glands. It can also be found in any other salivary tissue, either as an isolated cellular change — a hyperplastic cystic or solid hyperplasia — or as a neoplasm. Formerly considered an effete and dying cell, the oncocyte is now considered a metabolically redirected cell whose mitochondrial assembly has responded to local or systemically controlled stimuli.[1-3]

Virtually all aerobic, eukaryotic cells contain mitochondria. The cells' mitochondrial population, the chondriome, typically consists of variable numbers of spherical and elongated organelles with lengths of up to 4 μm. The characteristic electron-optic appearance of mitochondria has changed little throughout 400 million years of evolution.[2] The structure consists of a pair of membranes, outer and inner, that enclose a matrix of variable electron density.[1-3] Projecting into the matrix, often perpendicular to the inner membrane, are cristae. Small granular structures are frequently located in the matrix together with ribosomes and mitochondrial DNA. Duplication of the mitochondrial assembly requires the participation of six elements: mitochondrial DNA, transfer RNAs, and ribosomes, and a cytoplasmic set of the same three species.[1-3]

Mitochondria have a crucial role in the energy transformation of aerobic cells. Collectively, the matrix space and the inner mitochondrial membrane contain the full repertoire of enzymes required for mitochondrial function, which is to mediate the aerobic oxidation of pyruvate, fatty acids, and amino acids to form carbon dioxide and water.[1] The oxidations are coupled to the synthesis of adenosine triphosphate from adenosine diphosphate and inorganic phosphate. It is the capability to produce relatively large amounts of adenosine triphosphate at great speed from carbohydrates, fat, and protein that is the key functional feature of mitochondria.[1-3]

There is no question that modifications in the basic mitochondrial form and number are responses to changes in cell cycle or cell activity. Nor is there a question about the indispensable role of mitochondrial energetics in a cell's continuing existence. The relationships among number of mitochondria, their size, and their complexity seem to ratify the metabolic capability of cells to adapt to changes in their activity states — either in normal physiologic variation or as a consequence of abnormal demands.

TABLE 1. ONCOCYTES AND MAJOR SALIVARY GLANDS

Form of Histopathologic Presentation	*Comment*
Age-related "metaplasia" appearing as single cell oncocytes or in small isolated cell groups	Unusual before 50 yr of age, nearly always present after 65 yr
Oncocytic change in otherwise definable salivary gland tumors, notably pleomorphic adenomas	Less than 10%
Hyperplasias and benign neoplasias Multinodular oncocytosis Diffuse oncocytosis (not clinically nodular) Oncocytoma (solitary or multiple)	Less than 1% of all salivary gland tumors; all categories may be bilateral and are preponderantly parotid in origin
Malignant oncocytic (oncocytic carcinoma)	Less than 5% of all oncocytomas and 0.005% of all salivary gland tumors
Warthin's tumor	Up to 14% of all parotid gland epithelial tumors; may be multiple and bilateral

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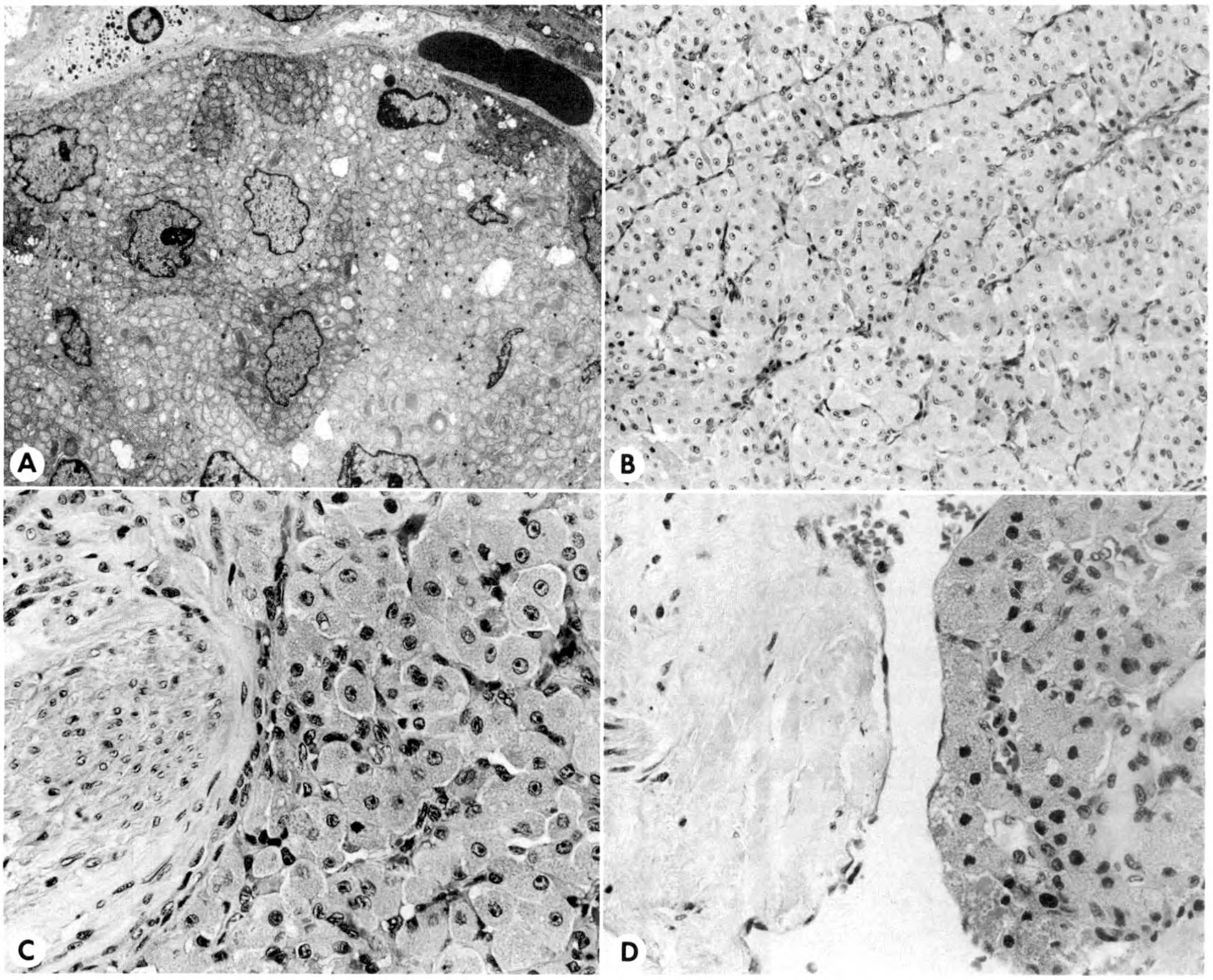
From the University of Texas M. D. Anderson Cancer Center, Houston, Texas.

REPRINTS — John G. Batsakis, MD, Dept of Pathology, University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030.



Oncocytic lesions. A) Electron micrograph of oncocytes in parotid gland oncocytoma (original x3,750). Each oncocyte is packed with mitochondria. B) Oncocytoma of parotid gland composed of closely packed oncocytes with their typical eosinophilic, finely granular cytoplasm (H & E, original x120). C) Oncocytic tumor of submandibular gland (H & E, original x240). Tumor cells are encroaching on but not invading nerve. Tumor had recurred twice. D) Intravascular extension of tumor in C (H & E, original x220). There is minimal cytomorphologic atypia of this clinically aggressive oncocytoma.

There is, however, not a firm transfer of mitochondrial form to the complex *functional* process of oxidative phosphorylation.[1-3] The increased number and size of the mitochondria with changes in the cristae seen in cells such as the salivary oncocyte may occur in order to compensate for defects in respiratory and other metabolic pathways; an estimated 60% of the cytoplasmic volume of oncocytoma cells is occupied by mitochondria[4] (see Figure, A). Other neoplasms, especially those with high glycolytic capabilities, have a paucity of mitochondria. Presumably, such neoplasms have changed to other (nonmitochondrial) forms of energy production.[1,2]

Table 2 gives the cellular characteristics of the salivary gland oncocyte. The presence of these should eliminate confusion of oncocytic lesions with oncocytoid ones.[5,6] Fine-structural studies have demonstrated that several other intracytoplasmic structures may impart an appearance similar to the oncocyte's, ie, smooth endoplasmic reticulum, dense lysosomal-like bodies, and secretory granules. To qualify as an oncocyte, a cell should 1) appear after the gland in which it occurs has reached histologic maturity, 2) manifest a high level of oxidative activity, 3) possess an unusually large number of mitochondria (these may be increased in size, show considerable pleomorphism, and contain glycogen and/or dense matrical inclusions), and 4) have no or regressed special cytoarchitectural features such as basal infolding and brush borders.[5-7] Electron microscopic demonstration of an excess of mitochondria is definitive and has a greater reliability than the histochemical reactions, one or more of which may be negative. Whether a myoepithelial oncocyte participates in oncocytomas is debatable and unlikely.[8,9]

In the clinicopathologic contexts given in Table 1, the oncocytic lesions should not be difficult to distinguish from oncocytoid lesions. Salivary duct

TABLE 2. CELLULAR CHARACTERISTICS OF SALIVARY GLAND ONCOCYTE

Hematoxylin and Eosin Appearance	*Histochemical Reactions*	*Electron Microscopic Appearance*
Cellular enlargement (10 to 15 μm)	PTAH and BAAF stains demonstrate numerous mitochondrial clumps	Marked increase in mitochondria; often with swollen, bizarre form
Eosinophilic cytoplasm variably filled with acidophilic granules	Increased activity of enzymes usually associated with microsomes or other cytoplasmic fractions	β-type glycogen in cytoplasmic matrix and in granular deposits in mitochondria
Coalescence of granules may produce pale, dark, or homogeneous (colloid) cytoplasm	Strong Luxol-fast blue reaction	Paucity of other organelles
Postremoval artifacts and cytoplasmic glycogen may produce optically clear cytoplasm	Metachromasia with thionin and cresyl violet	Desmosomal attachment between oncocytes
Organoid, solid, trabecular growth pattern	Glycogen-positive with PAS stain	
Nuclei centrally or minimally eccentrically placed; nucleoli not prominent	Absent to minimal intracellular mucin	

PTAH — phosphotungstic acid-hematoxylin, BAAF — Bensley's acid-aniline fuchsin, PAS — periodic acid-Schiff.

carcinoma, the high-grade adenocarcinoma most often found in the parotid glands of elderly men, is an oncocytoid neoplasm with its own distinctive histomorphology and should not be confused with oncocytic neoplasms. The same applies to intermediate-grade mucoepidermoid carcinomas, wherein the eosinophilic intermediate cell populations may be oncocytoid, and also to plasmacytoid (hyaline cell) myoepithelial cells. At the opposite end of the oncocytic spectrum is the clear-cell change that is secondary to an accumulation of glycogen or to a postremoval artifact.[10] If pronounced, the optical clarity of the cells may suggest a metastatic renal cell carcinoma, a primary clear cell carcinoma, or less likely, an acinic cell carcinoma.

Two clinical features are typical of oncocytic lesions of the major salivary glands: 1) a parotid gland preponderance and 2) the usually benign course of the lesions.[11-17] From a histopathologic viewpoint, the distinction between an oncocytic hyperplasia and a neoplasm of oncocytes can be difficult to define, especially in glands with clinically or surgically evident multiple nodules.[11,13,14,18] Bilaterality and an association with a diffusely focal oncocytic change in the involved glands arguably favor a hyperplasia. In general, hyperplastic lesions are less organized and circumscribed, are lobular rather than lobar, and do not manifest a single histologically dominant nodule. Oncocytic change in otherwise classifiable salivary gland neoplasms is most often seen in pleomorphic adenomas. Less often, oncocytes may be components of acinic cell, mucoepidermoid, and ductal adenocarcinomas.

Oncocytomas represent less than 1% of the epithelial tumors of the major salivary glands and are preponderantly parotid neoplasms (Table 3[7,12,14-17]). Like oncocytosis and oncocytic hyperplasias, they are found most often in patients who are in their sixth to eighth decades of life. Averaging 3 to 4 cm in diameter, the typically brown-red oncocytoma is usually a solid and solitary tumor (may be bilateral) that is circumscribed or encapsulated. The capsule varies in thickness, definition, and completeness. Histologically there is a complete oncocytic transformation of acini and ducts to form a solid, trabecular growth in which residual salivary parenchyma is rarely seen (see Figure, A). There may be microcystic or, more rarely, macrocystic change. A papillary oncocytoma is rare in the major salivary glands. Its appearance is that of an exaggerated Warthin's tumor — without its lymphoid tissue.

Oncocytic carcinomas (malignant oncocytomas) represent no more than 5% of all oncocytomas, hence, only 0.005% of all epithelial salivary neoplasms.[19] The major salivary glands, particularly the parotid glands, are the sites of predilection, but oncocytic carcinomas have been reported as being intraoral and from the sinonasal tract.[19,20] Cellular pleomorphism or polymorphism along with nuclear enlargement and mitoses can be a cytohistologic finding in an oncocytic carcinoma, but should not be used as a sole criterion for malignancy. Minimal-deviation oncocytomas are capable of metastases, and indeed, seemingly innocuous oncocytomas with metastasis have been reported. Batsakis[21] and later Goode and Corio[19] emphasized that the diagnosis of oncocytic carcinoma should be judged principally on invasive features, eg, perineurial invasion, intravascular and intralymphatic extension, and invasion into soft tissues, including adjacent salivary gland parenchyma (see Figure; B,C). Metastatic deposits in regional lymph nodes are irrefutable evidence. Finally, too great a histologic difference from a conventional oncocytoma, especially if the neoplasm is conspicuously ductal, should persuade a surgical pathologist toward a diagnosis of nononcocytic malignancy.

Oncocytic lesions of the seromucous glands of the

TABLE 3. INCIDENCE OF ONCOCYTOMAS IN THE PAROTID GLAND

		Oncocytomas	
Author	*Total No. of Tumors*	*No.*	*%*
Buxton et al[15]	280	3	1.0
Eneroth[12]	802	4	0.5
Foote and Frazell[16]	877	1	0.1
Kirklin et al[17]	909	4	0.4
Blanck et al[14]	1,678	13	0.8
Tandler et al[7]	1,751*	12	0.7

*Includes all major salivary glands.

upper aerodigestive tracts are not as uncommon as data from laryngeal biopsy specimens (0.5% to 1.0%) would indicate.[22-24] A more acceptable estimate of prevalence is suggested by necropsy statistics on cystic oncocytic laryngeal lesions (22%) or by the finding of oncocytic linings in symptomatic saccular and ductal cysts of the larynx (11%).[22]

Intraoral and upper airway oncocytic lesions are most often ectatic ducts with a partial or complete oncocytic alteration of the duct cells. Less often, the oncocytes manifest a cystic adenomatous hyperplasia. Solid oncocytomas are rare and oncocytic carcinomas of minor salivary glands are the most rare.[20,25] Only size and location of the benign, nonneoplastic, cystic, oncocytic lesions distinguish those that are symptomatic from incidental histologic findings. In the airway, the larynx leads for both categories, followed by the nasopharynx and sinonasal spaces, in that order. The supraglottic larynx, particularly the ventricles and false cords, is a site of predilection.[22]

Predictions of the biologic behavior of oncocytomas are hampered not only by their low frequency but also by difficulties attendant to distinguishing neoplastic lesions from hyperplastic ones, the tendency to multifocal growth, and a sometimes aggressive course by oncocytomas lacking conventional histologic evidence of malignancy. A not-too-dissimilar problem exists with the oncocyte's cousin, the Hürthle cell of the thyroid. Given these problems for the surgical pathologist, the expedient categorization into three groups suggested by Gray et al[11] seems most fitting. These workers, using gross, microscopic, and clinical features, place oncocytic neoplasms into benign, benign but locally aggressive, and malignant categories. With progression through the three types there is an increased recurrence rate and, with malignant oncocytomas, the demonstrated ability to metastasize locally and to distant sites. Not unexpected, tumor size and completeness of removal appear to be directly related to outcome. Goode and Corio[19] have indicated that oncocytic carcinomas smaller than 2 cm seem to offer a better prognosis. Declaration of malignancy in terms of metastases to cervical lymph nodes is usually early but can be delayed. While a short-term prognosis may appear to be good, the long-term (5 years or more) outlook is poor.[11,19,21] The histologically benign yet locally aggressive oncocytomas have a predilection for the sinonasal tract, in which the solid neoplasms manifest local invasion of bone and soft tissues but no metastatic capability.[11,26]

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LETTERS TO THE EDITOR

To the Editor:

I read with great interest the article "Clinical Diagnosis of Anterior Inferior Cerebellar Artery Thrombosis: Autopsy and Temporal Bone Histopathologic Study" (*Ann Otol Rhinol Laryngol* 1990;99:261-72) by Dr R. Hinojosa and Dr R. I. Kohut. I was very surprised to see their comment that patients who suffer from anterior inferior cerebellar artery (AICA) thrombosis rarely die from the event. This is completely contrary to the classic article written by W. J. Atkinson in 1949.[1]

Most of us who perform surgical procedures in the cerebellopontine angle are intimately familiar with Atkinson's classic article on the anatomy and distribution of the AICA. This artery is considered to be an end-artery, and occlusion or thrombosis of this vessel usually results in brain stem necrosis and death. Atkinson documents his conclusions with beautifully illustrated postmortem specimens of patients who died following acoustic tumor surgery in the early days of such endeavors. It is intriguing to me that the authors of the paper in the *Annals* failed to mention Atkinson's article. Instead, they focused upon the auditory and vestibular findings with patients who have thrombosis of the AICA.

There are a number of items in the article that would suggest that survival of AICA thrombosis is possible. This assumption would lead to the conclusion that the artery could be sacrificed during operation of the cerebellopontine angle, and I believe that most of us feel that this is completely erroneous. According to Atkinson's elegant studies, the only individuals who would likely survive AICA occlusion or thrombosis would be those individuals who have a very large posterior inferior cerebellar artery providing adequate collateral circulation for the AICA.

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REFERENCE

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To the Editor:

Dr Kohut and I read with interest the letter to you from Dr James E. Benecke, Jr, in relation to our paper regarding the histopathologic findings in an isolated thrombosis of the anterior inferior cerebellar artery (AICA).

Dr Benecke's main concern is the apparent conflict between our statement that patients having an AICA thrombosis rarely die from the event, and Atkinson's conclusion that severe consequences (death) result from clipping (occluding) the AICA during posterior fossa surgery.

Both statements are true. Adams's[1] report of 1943 indicates that patients having a thrombosis of the AICA tend not to die. As Dr Benecke states, Atkinson indicates that during posterior fossa surgery acute surgical occlusion results in death. It is probable that the variable of acute occlusion by surgical means is the difference between these two reports, which explains the apparent conflicts.

We agree that surgical procedures of the posterior fossa should be so executed as to avoid injury to the AICA. We also wonder if there are any differences between Atkinson's results using the surgical techniques of the 1940s and the results now obtained in which occlusion unavoidably occurs with use of our new neurotologic techniques and modern medical resources. The same question can be posed of Adams's results concerning spontaneous thrombosis of the AICA, again comparing the medical methods of the 1940s with today's techniques.

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REFERENCE

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To the Editor:

Thomsen and Koltai (Sternocleidomastoid Tumor of Infancy, *Ann Otol Rhinol Laryngol* 1989;98:955-9) stressed that sternocleidomastoid tumor might be an intrauterine phenomenon because of its association with other congenital lesions such as hip dysplasia. It is also important that not all the affected children have a history of birth trauma.

To emphasize the authors' point of view, we would like to report on a child with a right sternocleidomastoid tumor palpable since her birth. She was delivered by cesarean section because of transverse position with a birth weight of 2,480 g after 41 weeks of gestation. She had right torticollis and an asymmetric face with dolichocephaly. In addition she had a small ventricular septal defect and pelvic obliquity.

She was treated conservatively with passive stretching of the neck and at her present age of 7 months only mild improvement has been observed, making her a candidate for surgery in the future.

We agree with the authors that at least in some cases the sternocleidomastoid tumor is an intrauterine fibromatosis, perhaps one of several abnormalities present in the child.

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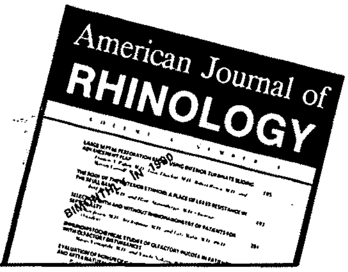

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RESEARCH GRANT AWARDS AND TRAINING FELLOWSHIPS

To Study Otosclerosis and Related Ear Disorders

The American Otological Society, Inc, through its Research Fund is offering **Research Grant Awards** and full-time **Research Training Fellowships** to study otosclerosis and related ear disorders in United States or Canadian institutions, July 1991 — June 1992. Proposals may include investigations of the management and pathogenesis of otosclerosis and underlying processes. Studies of middle ear biomechanics and sound transduction as they apply to otosclerosis will be considered.

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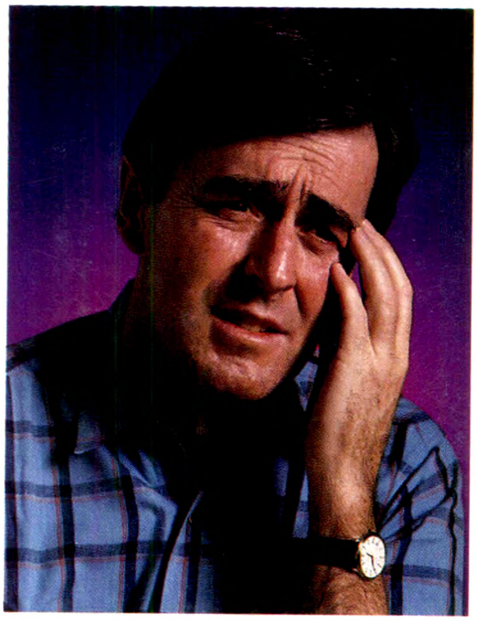

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- Stevens-Johnson syndrome, toxic epidermal necrolysis, and anaphylaxis have been reported rarely. Anaphylaxis may be more common in patients with a history of penicillin allergy.
- Gastrointestinal (mostly diarrhea): 2.5%.
- Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment.
- As with some penicillins and some other cephalosporins, transient hepatitis and cholestatic jaundice have been reported rarely.
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VOLUME 99 (11) — NOVEMBER 1990

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ANNALS OF HEAD & NECK MEDICINE & SURGERY

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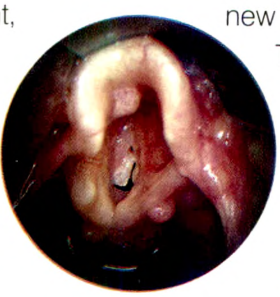

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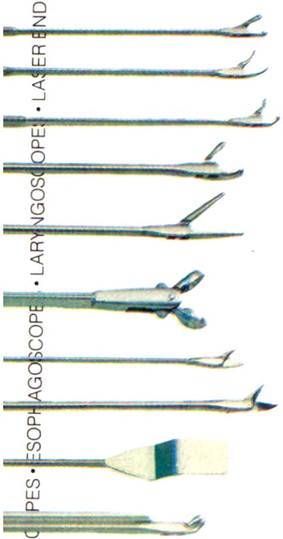

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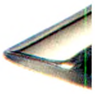

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ANNALS OF OTOLOGY, RHINOLOGY & LARYNGOLOGY (ISSN 0003-4894) is published monthly by Annals Publishing Company, 4507 Laclede Avenue, St Louis, MO 63108. Second-class postage paid at St Louis, Mo. POSTMASTER: Send address changes to Annals Publishing Company, 4507 Laclede Avenue, St Louis, MO 63108.

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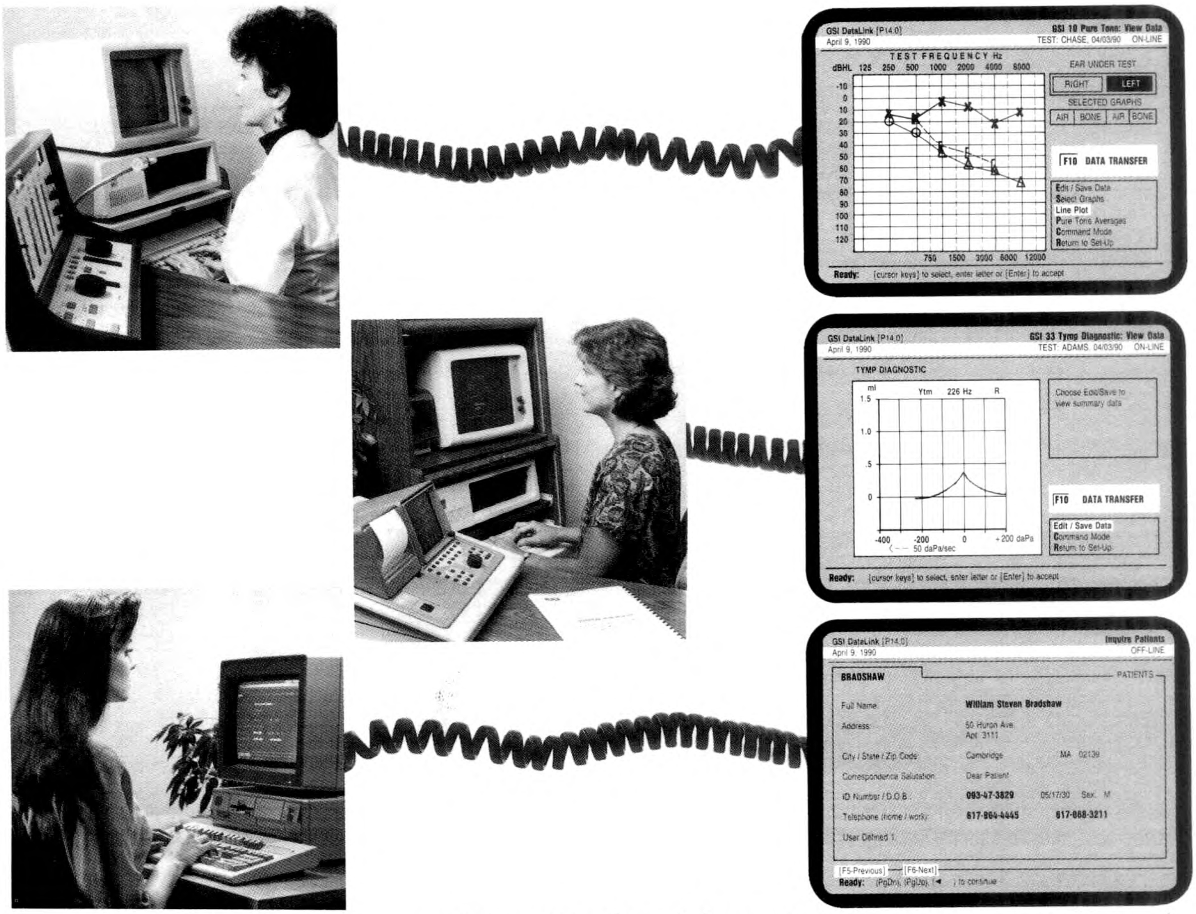

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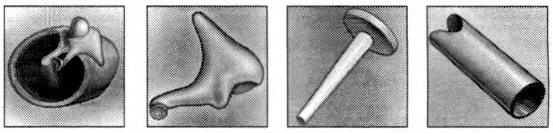

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Ann Otol Rhinol Laryngol 99:1990

DELAYED ENDOLYMPHATIC HYDROPS AND ITS RELATIONSHIP TO MENIERE'S DISEASE

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Delayed endolymphatic hydrops (EH) can be characterized as having ipsilateral and contralateral types. They are similar in that both have early and late phases of otologic symptoms and that the early phase is a profound hearing loss in one ear. The late phases differ, however, in that the ipsilateral type develops the symptoms of EH (episodic vertigo) in the deaf ear and the contralateral type develops the symptoms of EH (fluctuating hearing loss and/or episodic vertigo) in the hearing ear. In more than half the cases of both types of delayed EH, the profound hearing losses in the early phase are simply discovered to be present in early childhood without a known time of onset. The temporal bones of two patients with contralateral delayed EH show pathologic changes in the deaf ears that are similar to those known to occur in mumps and measles labyrinthitis, whereas the pathologic changes in the hearing ears are similar to those known to occur in Meniere's disease. These observations support the proposition that Meniere's disease may occur as a delayed sequela of inner ear damage sustained during an attack of subclinical viral labyrinthitis occurring in childhood.

KEY WORDS — delayed endolymphatic hydrops, endolymphatic hydrops, Meniere's disease, temporal bone pathology.

INTRODUCTION

In this paper we present our clinical experiences with delayed endolymphatic hydrops (EH), including the pathologic findings in the temporal bones of two cases, and suggest an etiologic relationship to Meniere's disease. The clinical manifestations of delayed EH consist of an early event characterized by the profound loss of hearing in one ear and a late event presenting with symptoms of EH in the same ear or the opposite ear. Meniere's disease, on the other hand, differs in that EH develops in one or both ears that previously had normal auditory and vestibular function.

We distinguish an ipsilateral form of delayed EH in which episodic vertigo results from EH in the deaf ear and a contralateral form in which fluctuating hearing loss, sometimes with episodic vertigo, results from EH in the opposite ear that previously had normal hearing.

In 1975 Wolfson and Leiberman[1] reported five cases, all of which presented an ipsilateral delayed EH. The hearing losses were discovered in childhood in two, were attributed to mumps in two, and consisted of sudden deafness in one. Delays of onset ranged from 9 to 24 years.

In the same year, Nadol et al[2] presented 12 cases of delayed EH, 10 of which were of the ipsilateral type and 2 of which consisted of early hearing losses in both ears. Among the suspected causes for hearing loss were mumps in 2, upper respiratory tract infection in 2, head trauma in 1, basal skull fracture in 1, and congenital or neonatal onset of unknown cause in 6. Delay of onset varied from 1 to 68 years (average, 28 years). Labyrinthectomy was performed on 10 patients. Analysis of perilymph removed by footplate tap in 4 cases revealed values consistent with endolymph in 2; this finding is considered to be diagnostic for EH.[3]

In 1978 Schuknecht[4] reported his experience with 12 ipsilateral cases and in addition presented 6 cases that exemplified the contralateral type of the disease. This group of cases was expanded to 22 ipsilateral cases and 21 contralateral cases in a 1985 report,[5] and in this current report to 31 ipsilateral and 31 contralateral.

Kamei[6] studied 89 patients with juvenile unilateral total deafness that were encountered during a 14-year period and found that episodic vertigo developed in 27 (30%). Three of the 27 patients also experienced fluctuating hearing loss in the opposite ear that previously had normal hearing.

In 1980 LeLiever and Barber[7] presented 18 cases of ipsilateral delayed EH. The delay between identification of the deafness and the onset of vertigo ranged from 6 to 50 years (average, 22.6 years). Measles or mumps was believed to have caused the deafness in 8 of the 18 cases. Six were treated by labyrinthectomy and 1 by endolymphatic saccotomy. Perilymph taps through the footplate in 7 ears revealed that 5 had electrolyte values consistent with endolymph.

Paparella and Mancini[8] reported on 37 patients with Meniere's-like symptoms after either acoustic trauma or head injury. In many cases the onset was delayed for some years after the insult had occurred.

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TABLE 1. IPSILATERAL DELAYED ENDOLYMPHATIC HYDROPS: HISTORIES (N = 31)

Early History				*Late History*				
					Caloric Response		*Labyrinthectomy*	
Patient	*Profound Hearing Loss*	*Age (yr)*	*Cause*	*Age at Onset of Episodic Vertigo (yr)*	*Ipsilateral Ear*	*Opposite Ear*	*Age*	*Year*
1	R	24	Mastoidectomy	46	N	N		
2	L	4	Head blow	16	DVR	N	23	1975
3	R	DIC	?	18	DVR	N	21	1976
4	L	DIC	?	32	DVR	N	37	1961
5	R	30	Sudden deafness	40	N	N		
6	R	DIC	?	45	DVR	N		
7	L	DIC	?	27	DVR	N	27	1973
8	L	DIC	Mumps	7	N	N	10	1966
9	R	DIC	Mumps	26	DVR	N		
10	R	DIC	?	47	NR	DVR		
11	L	DIC	?	19	DVR	N	20	1983
12	L	DIC	?	23	DVR	N	25	1982
13	R	DIC	?	14	DVR	N		
14	R	DIC	?	42	NR	N	42	1966
15	R	6	Head blow	30	N	N		
16	L	DIC	?	25	DVR	N	28	1970
17	R	9	Influenza	53	NR	N		
18	L	37	Sudden deafness	56	N	N		
19	R	50	Sudden deafness	56	DVR	N	61	1970
20	R	DIC	?	25	DVR	N		
21	L	8	Head blow	10	DVR	N	22	1970
22	L	55	Sudden deafness	67	DVR	N		
23	L	DIC	?	32	DVR	N	32	1987
24	L	DIC	?	25	NR	NR		
25	R	DIC	?	17	DVR	N	20	1988
26	L	DIC	Measles	78	DVR	N		
27	R	DIC	?	26	DVR	N	27	1986
28	R	13	?	17	N	N		
29	R	8	?	22	DVR	N		
30	R	DIC	?	18	DVR	DVR		
31	L	5	Temporal bone fracture	12	DVR	N	13	1989

DIC — discovered in childhood, N — normal, DVR — decreased vestibular response, NR — no response.

In a study of 400 senior officers in the Finnish Defense Forces, Ylikoski[9] found 18 cases of delayed hydrops syndrome. All 18 patients had been exposed to firearm noise in the 1950s and 1960s without ear protection.

Karmody[10] presented the clinical findings of four patients with congenital, bilateral, severe, sensorineural hearing losses who later developed episodic vertigo suggestive of EH. It is not clear that the hearing losses were congenital, and they may have been acquired in infancy. Such cases might be classified as bilateral delayed EH, as proposed by Schuknecht.[5]

In a recent report Hicks and Wright[11] presented eight cases of ipsilateral EH and seven cases of contralateral delayed EH. The delay of onset was 22.2 years for the ipsilateral cases and 18 years for the contralateral cases. All eight of their patients with unilateral disease underwent surgical procedures, with six having labyrinthectomy, one endolymphatic saccotomy, and one vestibular nerve section.

CLINICAL CASES

This study includes all cases of delayed EH presenting to the senior author (H.F.S.) from 1961 to 1989 and is updated to include new cases seen after the last report.[5] There are 31 cases that satisfy the criteria for the ipsilateral type, and an equal number for the contralateral type of delayed EH. The two types are similar in that they both have early and late phases of otologic symptoms, with both manifesting a profound unilateral sensorineural hearing loss in the early phase. The late phases differ, however, in that in one type symptomatic EH develops in the ipsilateral (deaf) ear, and in the other type it develops in the contralateral (hearing) ear.

Ipsilateral Delayed Endolymphatic Hydrops. The events relating to the unilateral profound sensorineural hearing losses appear in Table 1 and are summarized in Table 2. Eighteen of the 31 cases were simply discovered in early childhood at about the age of 4 years. Other presumed causes were sudden deafness in 4, head injury in 4, mumps in 2, and 1 each of measles, mastoidectomy, and influenza. The age of onset of profound unilateral hearing loss varied from 4 to 55 (average, 10) years. After intervals of 2 to 74 (average, 21.3) years, the late phase

TABLE 2. IPSILATERAL DELAYED ENDOLYMPHATIC HYDROPS: ONSET AND TIME DELAY VERSUS ETIOLOGY (N = 31)

	No. of Patients	*Mean Age at Onset of Profound Loss (yr)*	*Mean Age at Onset of Vertigo (yr)*	*Mean Time Delay (yr)*
Childhood onset, cause unknown	18	4±	26.3	22.3
Sudden deafness	4	43	54.7	11.7
Head injury	4	5.7	17	11.3
Mumps	2	4	16.5	12.5
Measles	1	4	78	74
Mastoidectomy	1	24	46	22
Influenza	1	9	53	44
Average		10	31.3	21.3
Range		4-55	7-78	2-74

appeared. It was characterized by episodic vertigo of the Meniere's type, that is, violent episodes of vertigo lasting several hours that were associated with nausea, vomiting, sweating, and sometimes diarrhea. Intervals between attacks varied from days to weeks or months.

All caloric tests were done by the senior author using the Kobrak method whereby 5 mL of water at 27°C is injected against the tympanic membrane during a period of 10 seconds with a syringe and a 20-gauge needle. The sensitivity of the vestibulo-ocular reflex is determined by timing the duration of nystagmus as well as judging the magnitudes of eye movement. The tests are done with the aid of Frenzel glasses in a darkened room. A comparison with the opposite, presumably normal ear increases the reliability of the tests. If no response is noted, 5 mL of ice water is used. The results of the caloric tests appear in Table 1 and are summarized in Table 3. Note that 21 of the 31 deaf ears had a decreased vestibular response and another 4 had no response to ice water.

Labyrinthectomies were performed in 15 of the 31 cases, and all were successful in relieving intractable episodic vertigo.

Contralateral Delayed Endolymphatic Hydrops. The events relating to the unilateral profound sensorineural hearing loss appear in Table 4 and are summarized in Table 5. Twenty-four of the 31 cases were discovered in childhood at about the age of 4 years. Other presumed causes were meningitis in 3, sudden deafness in 2, and later onset of unknown cause in 2. The age at onset of profound unilateral hearing loss ranged from 4 to 63 (average, 8.5) years. After time delays of 1 to 57 (average, 20.3) years, the late phase appeared. It was characterized by the onset of fluctuating hearing loss in the opposite, previously normal hearing ear. The fluctuations of hearing were identical to those occurring in Meniere's disease, beginning with fluctuations mainly for the low frequencies, progressing in some months or years to involve all frequencies, but often worse for the very low and high frequencies. Like patients with Meniere's disease, these patients have a pressure sensation and tinnitus in the ear that often occurs when there is a downward fluctuation of hearing. Episodic vertigo occurred in 15 of the 31 cases of contralateral delayed EH. It was the hearing loss, however, that was the most disabling and depressing symptom of this type of delayed EH.

TABLE 3. IPSILATERAL DELAYED ENDOLYMPHATIC HYDROPS: CALORIC RESPONSES (N = 31)

Caloric Responses	*Ear 1 Profound Loss*	*Ear 2 Normal Hearing*	*Labyrinthectomies Ear 1*
Normal	6	28	1
Decreased vestibular response	21	2	13
No response to ice water	4	1	1
Total	31	31	15

The caloric responses are shown in Table 4 and are summarized in Table 6. When one compares the caloric responses in the ipsilateral (Table 3) and contralateral cases (Table 6), it is evident that the contralateral cases show greater reductions. For example, the deaf ear showed no response to ice water in 4 cases of ipsilateral delayed EH, but showed no response in the deaf ear in 11 cases of contralateral delayed EH. This finding suggests that the deaf ear in the contralateral cases generally suffers greater pathologic changes in the vestibular labyrinth than the deaf ear of ipsilateral cases. The same can be said for the opposite ears, in which only 1 case of ipsilateral delayed EH showed no response to ice water caloric testing, whereas 12 of the contralateral cases showed no response. Table 4 also shows that the episodic vertigo occurred in 9 of 11 cases in which caloric responses were normal in the contralateral ear, but in only 1 of 12 cases in which there was no response to ice water testing. There were 9 patients in the contralateral delayed EH group who had no caloric response to ice water in either ear, and 4 of these had a history of ataxia manifested as clumsiness in childhood, difficulty walking in the dark, and/or oscillopsia.

TEMPORAL BONE PATHOLOGY

We have acquired the temporal bones of two persons who had contralateral delayed EH. The specimens have been prepared in the usual manner for light microscopic study, which is done by decalcification in trichloroacetic acid, embedding in celloidin, serial sectioning at a thickness of 20 μm, staining every 10th section with eosin and hematoxylin, and mounting on glass slides. Losses of hair cells and stria vascularis and pathologic changes in the tectorial membrane are plotted on two-dimensional graphic reconstructions of the cochleas. The tectorial membrane is judged to be functional or nonfunctional. It is considered nonfunctional if it is spherically deformed, atrophied, encapsulated, or missing. The stria vascularis is evaluated in terms of the estimated volume of missing strial tissue.

TABLE 4. CONTRALATERAL DELAYED ENDOLYMPHATIC HYDROPS: HISTORIES (N = 31)

	Early History			*Late History*					
							Caloric Response		
Patient	*Profound Hearing Loss*	*Age (yr)*	*Cause*	*Age at Onset of Symptoms in Contralateral Ear (yr)*	*Fluctuating Hearing*	*Episodic Vertigo*	*First Ear*	*Contra-lateral Ear*	*Ataxia*
1	R	DIC	?	14	+		NR	NR	
2	L	26	Sudden deafness	58	+		DVR	DVR	
3	L	DIC	?	17	+		NR	NR	+
4	L	DIC	?	5	+		DNT	DNT	
5	R	DIC	?	8	+	+	N	DVR	
6	L	DIC	?	41	+	+	N	N	
7	R	DIC	?	5	+		NR	NR	+
8	R	DIC	?	16	+		DVR	N	
9	L	DIC	?	29	+	+	NR	N	
10	L	DIC	?	14	+	+	DVR	DVR	
11	L	DIC	?	10	+	+	NR	NR	+
12	L	DIC	?	15	+	+	N	N	
13	R	DIC	?	40	+		NR	NR	
14	L	63	Sudden deafness	69	+	+	DVR	N	
15	R	DIC	?	29	+		DVR	NR	
16	R	DIC	?	21	+		NR	NR	
17	L	4	Meningitis	34	+		N	NR	
18	L	DIC	?	16	+	+	DVR	N	
19	L	DIC	?	48	+	+	N	N	
20	R	DIC	?	5	+		NR	NR	+
21	R	15	Meningitis	42	+		NR	NR	
22	L	DIC	?	61	+	+	DVR	DVR	
23	R	DIC	?	25	+		DNT	DNT	
24	R	4	Meningitis	41	+	+	N	N	
25	R	DIC	?	26	+		DVR	NR	
26	R	47	?	62	+	+	NR	DVR	
27	R	DIC	?	27	+		DVR	N	
28	L	DIC	?	20	+		NR	NR	
29	L	10	?	32	+	+	DVR	N	
30	R	DIC	?	28	+	+	DVR	N	
31	R	DIC	?	35	+	+	N	DVR	

All cases of meningitis were of bacterial origin.

DIC — discovered in childhood, NR — no response, DVR — decreased vestibular response, N — normal, DNT — did not test.

The cochlear neurons are counted and plotted on two-dimensional reconstructions of the spiral ganglia. Final counts are determined by multiplying by 10 as well as a correction factor of 0.9 to account for bisected neurons. The neuronal populations are totaled for each of four segments of the cochlea and are plotted as percent loss compared to the average populations of age-matched controls as described by Otte et al.[12] Thus, the organ of Corti is innervated by segment 1 (0 to 6 mm), segment 2 (6 to 15 mm), segment 3 (15 to 22 mm), and segment 4 (22 to 32 mm). The data are transferred from the reconstructions to cytocochleograms with black filling indicating losses.

The corresponding audiograms are plotted on parallel coordinates with the cytocochleograms. The frequencies are located on the abscissa in accordance with the spatial distribution of their points of maximum resonance within the cochlea. This anatomic frequency scale has been derived from 37 cochleas having abrupt audiometric losses and sharply marginated areas of hair cell loss (H.F.S., unpublished data, 1989).

CASE REPORTS

CASE 1

The patient was first examined at the otolaryngology department of the Massachusetts Eye and Ear Infirmary at the age of 31, stating that he had had a profound hearing loss in his left ear all of his life that he believed was caused by mumps. He also complained of fluctuating hearing and constant low-pitched tinnitus in his right ear. Audiometric

TABLE 5. CONTRALATERAL DELAYED ENDOLYMPHATIC HYDROPS: ONSET AND TIME DELAY VERSUS ETIOLOGY (N = 31)

		Mean Age (yr) at Onset of		
	No. of Patients	*Profound Loss in Ear 1*	*Fluctuating Loss in Ear 2*	*Time Delay (yr)*
Childhood onset, cause unknown	24	4±	23.1	19.1
Bacterial meningitis	3	7.6	39	31.4
Sudden deafness	2	44.5	60.5	16
Adult onset, cause unknown	2	28.5	47	18.5
Average		8.5	28.8	20.3
Range		4-63	5-69	1-57

TABLE 6. CONTRALATERAL DELAYED ENDOLYMPHATIC HYDROPS: CALORIC RESPONSES (N = 31)

Caloric Responses	*Ear 1*	*Ear 2*
Normal	7	11
Decreased vestibular response	11	6
No response to ice water	11	12*
Did not test	2	2

*Bilateral in 9.

studies revealed normal hearing on the right side with 100% discrimination and a profound left-sided sensorineural hearing loss. Otoscopy revealed normal tympanic membranes. The automated reagin test for syphilis was nonreactive. At the age of 34 an audiogram revealed a low-tone sensorineural hearing loss in the right ear and profound hearing loss in the left ear. Discrimination in the right ear was 100%. There was no history of vestibular symptoms, but he continued to complain of tinnitus in his right ear. Auditory evoked response tests showed all wave latencies to be within normal tolerance limits.

Five months later, at the age of 35, he fell to the floor, vomited, became cyanotic, and experienced cardiac arrest. An emergency medical team was promptly summoned, but was unable to revive him. Autopsy revealed tracheobronchial aspiration of gastric contents, bilateral renal congestion, slight pulmonary edema, and a patent cardiac foramen ovale.

Histopathology of Right Ear. There is EH in the apical region of the cochlea and in the upper basal turn (Fig 1B,C and Table 7). The hair cells, stria vascularis, and tectorial membrane show atrophic changes only at the extreme basal end of the cochlea. There is a slight loss of cochlear neurons in segment 1.

There is hydrops of the saccule, although the membranous wall does not reach the stapedial footplate (Fig 1B). The anterior third of the saccular macula shows atrophic changes characterized by atrophy of the sensory epithelium, partial cellular encapsulation of the otolithic membrane, and a granular basophilic plaque overlying the supporting network of the macular epithelium (Fig 1D). The utricle is dilated, and the walls are in contact with the bony walls of the upper part of the vestibule. The macula of the utricle is normal. The common crus is dilated. The cristae and the semicircular ducts appear normal.

The endolymphatic duct is blocked and in part of its course appears as a strand of epithelial cells without a lumen (Fig 1E).

Histopathology of Left Ear. There is moderately severe EH, with Reissner's membrane passing through the middle region of the scala vestibuli in all turns of the cochlea (Fig 2B,C and Table 7). There is a near-total loss of hair cells in the basal half and almost 50% in the apical half of the cochlea. In much of the basal turn the organ of Corti either consists of a mound of undifferentiated cells or is totally missing. The tectorial membrane is spherically deformed and encapsulated throughout turn 1 and is missing in turns 2 and 3. The stria vascularis shows patchy atrophy in the apical half of the cochlea. There is a slight loss of cochlear neurons in segments 2, 3, and 4.

The saccule shows severe EH. There is total de-

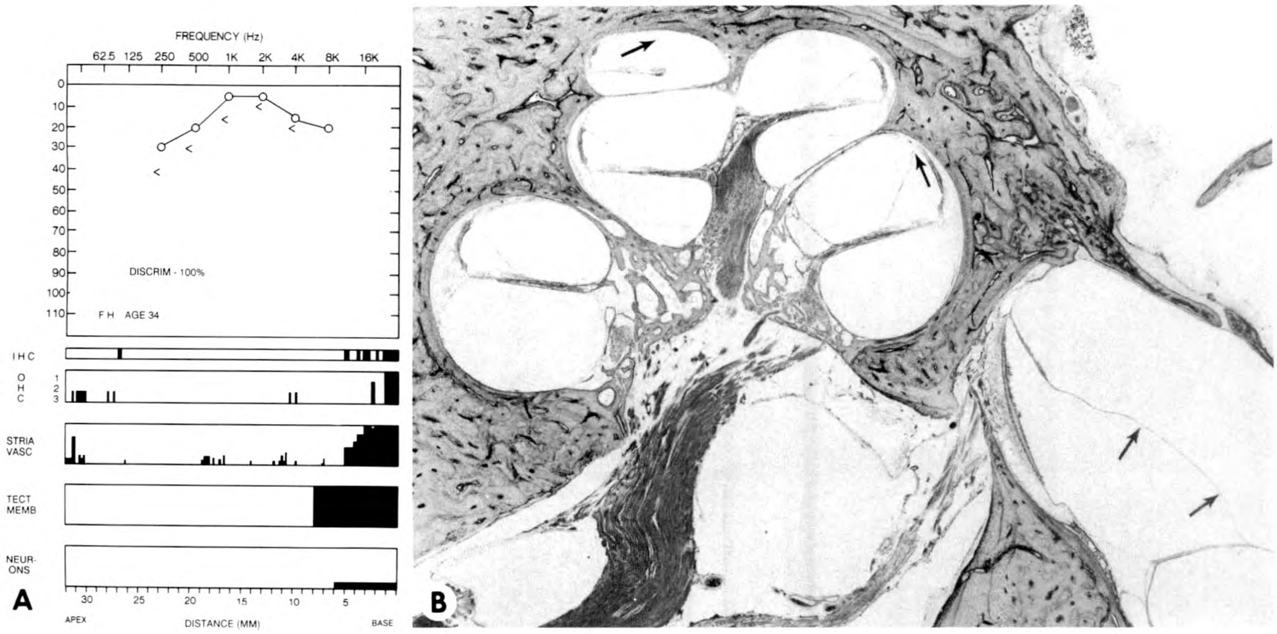

Fig 1. (Case 1) Right ear. A) Audiogram and cytocochleogram. Frequencies are plotted on data-based anatomic frequency scale. Distance is measured from basal end of cochlea. Black filling in bars represents percentage of missing or nonfunctional elements. B) Mild endolymphatic hydrops in upper basal and apical turns of cochlea and saccule (arrows). (Continued on next page.)

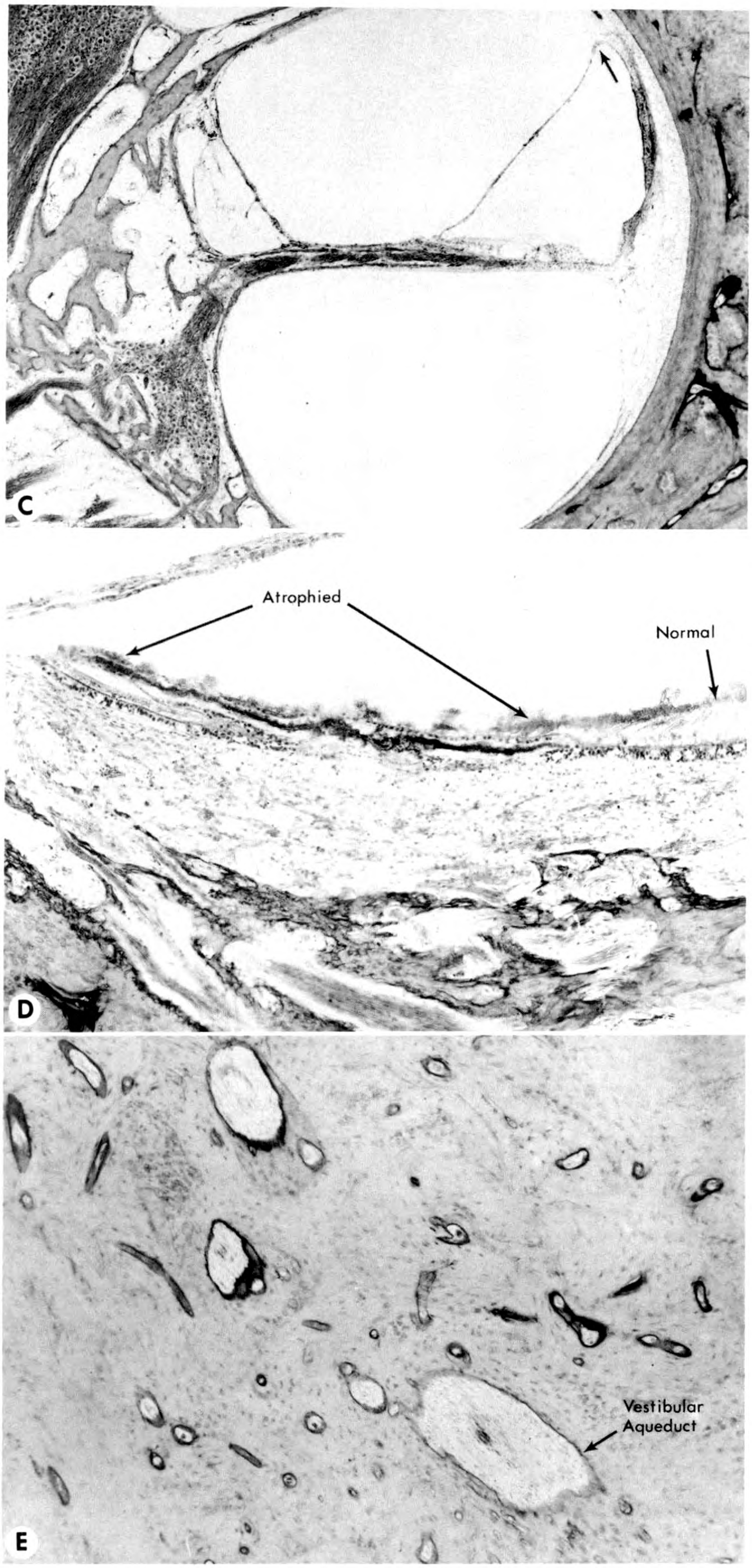

Fig 1 (continued). C) Upper basal turn of B showing mild endolymphatic hydrops (arrow). Organ of Corti, stria vascularis, and cochlear neuronal population are normal. D) Atrophy of anterior third of saccular macula. Sensory epithelium shows loss of hair cells, and otolithic membrane has degenerated into irregular basophilic plaque that has been partly encapsulated by cells. E) Endolymphatic duct has degenerated into strand of epithelial cells without lumen.

TABLE 7. CONTRALATERAL DELAYED ENDOLYMPHATIC HYDROPS: PERCENT INCREASE COCHLEAR ENDOLYMPHATIC HYDROPS

	Case 1		*Case 2*	
Cochlear Turn	*Right*	*Left*	*Right*	*Left*
Lower basal	0	162.6	17.4	217.3
Upper basal	21.7	207.3	19.1	278.1
Lower middle	0	166.4	20.0	289.9
Upper middle	0	93.3	11.5	219.5
Apical	132.4	258.1	58.5	214.8
Average		177.5	25.3	243.9

Computer-aided measurements (%) of increases in cross-sectional areas of cochlear ducts in single midmodiolar sections of cochleas.

generation of the sensory epithelium, with no hair cells remaining. There are islands of supporting cells, and there are scattered basophilic deposits partially encapsulated by undifferentiated cells (Fig 2D). The utricle shows severe EH, and the macula is severely atrophic. The sensory epithelium is devoid of hair cells and contains only irregular patches of supporting cells, interspersed with areas of fibrous proliferation and basophilic inclusions. All cristae show severe atrophic change, with total loss of hair cells and most of the supporting cells, as well as scattered basophilic inclusions. The stroma of the cristae also show loss of cellularity. The ampullae are greatly dilated and distorted. Most of the lateral semicircular duct is collapsed. There is a loss of approximately 50% of the vestibular neurons and nerve fibers.

The endolymphatic duct is blocked and in part of its course consists of a central strand of epithelial cells without a lumen (Fig 2E). There is a partial loss of epithelium in the endolymphatic sac.

CASE 2

This woman was known to have had a profound hearing loss in her left ear that was first noticed in early childhood. Between the ages of 50 and 70 she was examined on several occasions by an otolaryngologist, whose records show that she had a fluctuating hearing loss in her right ear. At age 57 it was noted that she had "vertigo." A pure tone air conduction audiogram at age 60 showed responses at 80 to 90 dB in the left ear. Masking was not used, and it is probable that this is a "shadow curve" of the opposite ear and that this ear was in fact profoundly deaf. The right ear showed a moderate hearing loss, worse for the very low and high frequencies. The patient died at age 73 of heart failure.

Histopathology of Right Ear. There is mild hydrops of the cochlear duct that is most evident in the apical and upper basal turns (Fig 3B and Table 7). In the basal 5 mm the hair cells and tectorial membrane are missing. The stria vascularis shows 20% to 60% atrophy throughout the cochlea, which is consistent with strial presbycusis. The cochlear neuronal population is normal.

The saccule is greatly dilated and its wall is in contact with the footplate and lateral wall of the vestibule; however, the saccular macula appears normal. The inferior part of the utricle is dilated, but the utricular macula is normal. The cristae, ampullae, and semicircular ducts appear normal. The vestibular nerve trunk has been avulsed; however, the nerve fiber populations in the cribrose areas appear normal. The endolymphatic duct is patent and the endolymphatic sac is unremarkable.

Histopathology of Left Ear. There is severe EH of the cochlear duct (Fig 4B and Table 7). In most areas of all three turns, Reissner's membrane ap-

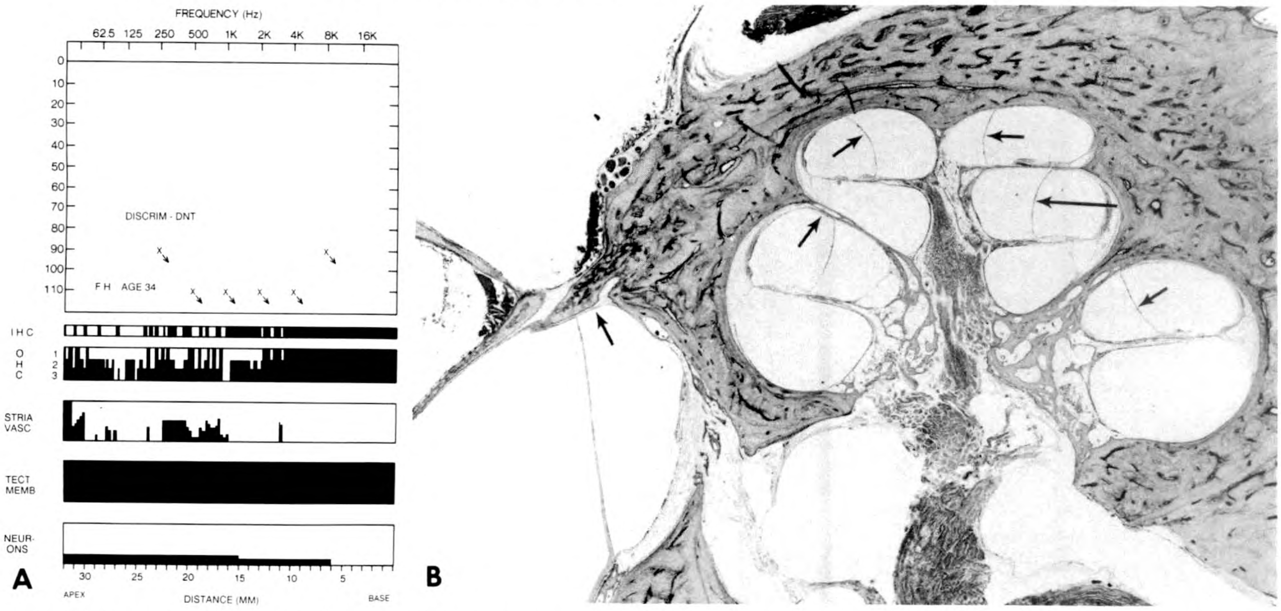

Fig 2. (Case 1) Left ear. A) Audiogram and cytocochleogram. There is near-total loss of hair cells in basal half and about 50% loss in apical half of cochlea. Tectorial membrane is totally nonfunctional. B) Moderately severe hydrops of cochlear duct and saccule (arrows). (Continued on next page.)

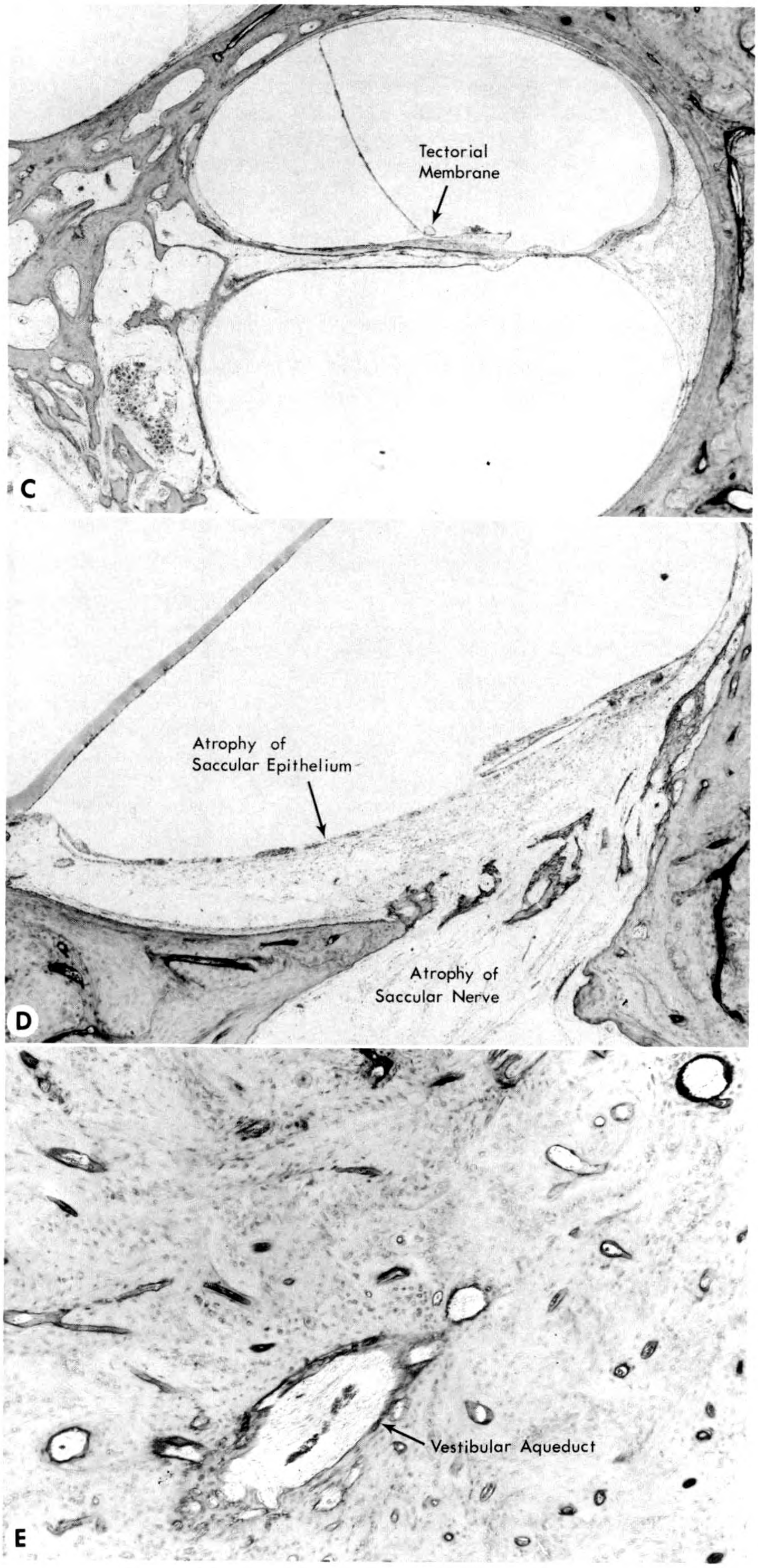

Fig 2 (continued). C) Lower basal turn showing endolymphatic hydrops of cochlear duct, loss of hair cells, atrophy of stria vascularis, and spherical deformation and cellular encapsulation of tectorial membrane. D) Saccular epithelium has totally degenerated, with no hair cells remaining. Otolithic membrane is missing or has degenerated into basophilic deposits. There is severe loss of nerve fibers. E) Endolymphatic duct has degenerated into strand of epithelial cells without lumen.

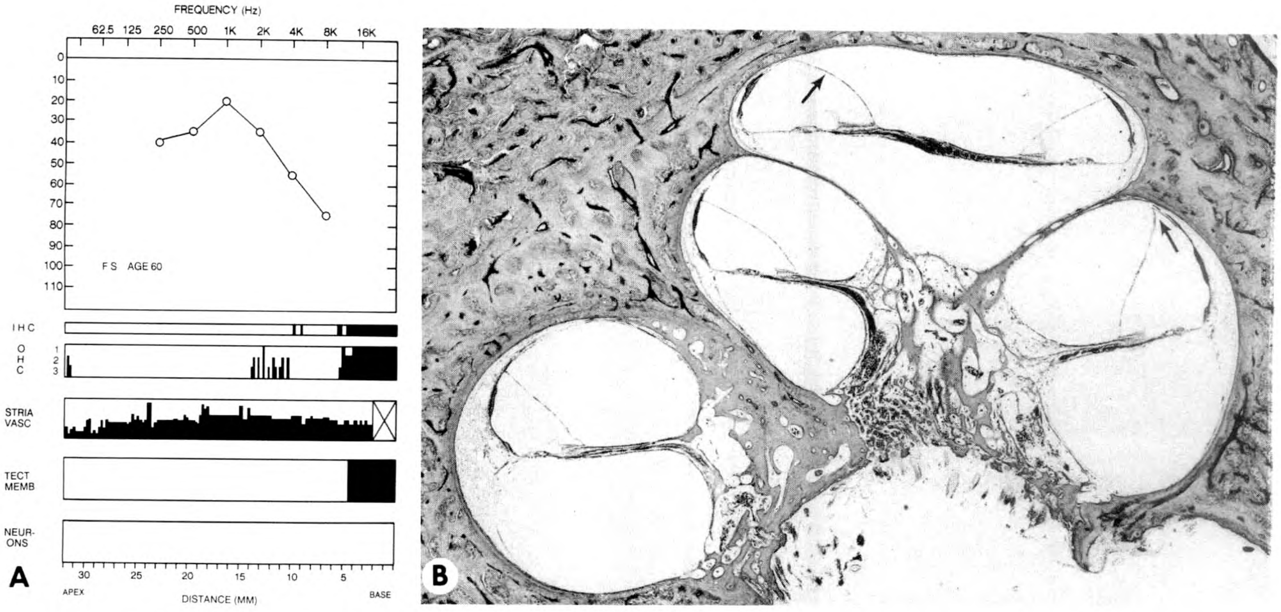

Fig 3. (Case 2) Right ear. A) Audiogram and cytocochleogram. Hair cells and tectorial membrane are missing in basal 5 mm of cochlea. There is moderately severe atrophy of stria vascularis. B) Cochlea shows endolymphatic hydrops of upper basal and apical turns (arrows). There is partial atrophy of stria vascularis in all turns. Hair cell and neuronal populations appear normal.

pears atrophic and is adherent to the bony walls of the scala vestibuli. In the basal 20 mm of the cochlea, the organ of Corti either is missing or consists of a small mound of undifferentiated epithelial cells without hair cells. Both inner and outer hair cells are present but in diminished numbers in the apical 12 mm. The stria vascularis is totally atrophied in the basal 23 mm and about 50% atrophied in the apical 9 mm. The tectorial membrane is either missing or spherically deformed and encapsulated in all turns. There is a moderate loss of cochlear neurons that is greatest in segment 3. The cell bodies that remain are shrunken and have lost their dendritic fibers.

The saccule is greatly dilated, and its wall is atrophied and is in contact with the footplate and lateral wall of the vestibule. The saccular macula is severely atrophied, with only patchy areas of undifferentiated epithelium remaining. The utricle and nonampullated end of the lateral semicircular duct are greatly dilated. The utricular macula and cristae appear normal. The vestibular nerve trunks have been avulsed, but the nerve fibers in the cribrose areas are present and appear normal. The endolymphatic duct is patent and the endolymphatic sac is unremarkable.

DISCUSSION

The total evidence from clinical observations and pathologic studies strongly supports the concept that delayed EH is a clinical entity. While certain insults such as acoustic trauma, head blow, temporal bone fracture, sudden deafness, mumps, measles, and upper respiratory tract infection have been implicated as causative factors, there are many cases in which no definite etiologic agent can be identified.

The histopathologic findings in the deaf ears in cases 1 and 2 are consistent with viral labyrinthitis in that the changes are similar to those known to occur in mumps[13] and measles[14,15] deafness. The specific features are various degrees of atrophy of the sense organs, followed by retrograde neuronal degeneration and EH, all occurring without a fibroproliferative or osseous reaction. It seems quite probable, therefore, that those clinical cases that are listed as discovered in childhood in Tables 1 and 4 are caused by viral labyrinthitis occurring in infancy. There is evidence from immunologic studies using an IgM antibody test that unilateral hearing loss occurring in childhood is frequently caused by subclinical mumps.[16] Westmore et al[17] cultured mumps virus from a sample of perilymph collected 5 days after the onset of sudden deafness.

The contralateral ears in cases 1 and 2, on the other hand, which exhibited fluctuating hearing losses, have the classic pathologic changes of Meniere's disease. The specific pathologic feature is EH of various degrees, with little or no atrophy of the sense organs or neurons. It seems highly probable that these ears that developed delayed EH had suffered a viral attack on the occasion that the opposite ear was rendered deaf. This probability is supported by the observation that some of the contralateral cases (Table 4) had evidence of bilateral loss of vestibular function from early childhood prior to the onset of hearing loss in the contralateral ear. In many cases, however, the caloric responses were normal or slightly reduced, and the insult to the contralateral ear was truly subclinical.

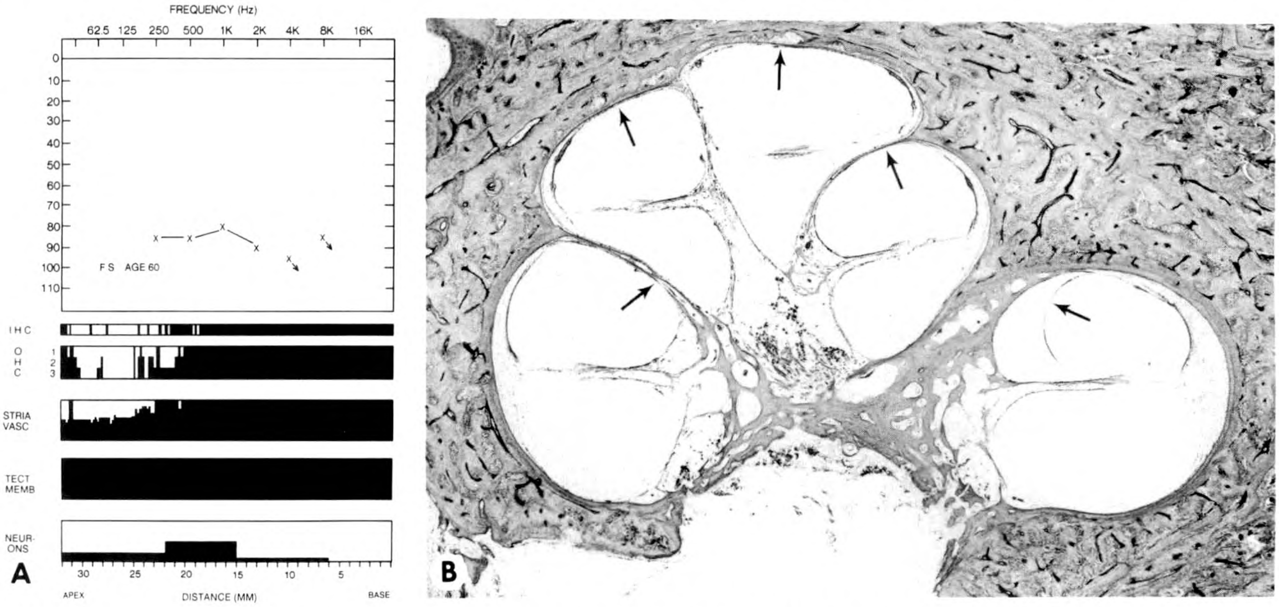

Fig 4. (Case 2) Left ear. A) Audiogram and cytocochleogram. In basal 20 mm of cochlea, hair cells are missing. Tectorial membrane is nonfunctional throughout. Stria vascularis is totally atrophied in basal 23 mm of cochlea. There is mild loss of cochlear neurons in segments 2, 3, and 4. B) Severe endolymphatic hydrops in all three turns of cochlea (arrows). There is severe atrophy of organ of Corti, stria vascularis, and tectorial membrane. There is moderate loss of cochlear neurons; cell bodies that remain are shrunken and have lost their dendrites.

Assuming that viral labyrinthitis can occur in infants as a subclinical disease that results in delayed EH, we may have an explanation for Meniere's disease. Viewed in this context, the disease entity known as delayed EH becomes the missing link in understanding the pathogenesis of Meniere's disease.

CONCLUSIONS

1. Endolymphatic hydrops may occur as a delayed reaction in ears rendered deaf for a variety of causes and may cause episodic vertigo if the vestibular sense organs are functional. This disorder is known as ipsilateral delayed EH.

2. Endolymphatic hydrops may occur as a delayed reaction in ears opposite to deaf ears and may cause fluctuating hearing loss, with or without episodic vertigo. This disorder is known as contralateral delayed EH.

3. Unilateral profound deafness of unknown cause was discovered in childhood in 18 of 31 cases of ipsilateral delayed EH and 24 of 31 cases of contralateral delayed EH.

4. The histopathologic findings in the profoundly deaf ears in two cases of contralateral delayed EH of unknown cause are like those of measles and mumps labyrinthitis.

5. The histopathologic findings in the opposite ears of these two cases are similar to the pathologic changes occurring in Meniere's disease.

6. These observations support the concept that delayed EH and Meniere's disease are related disorders caused predominantly by viral labyrinthitis.

7. It is proposed that the clinical expression of these disorders is a variable of severity of involvement, the most severe being immediate total loss of auditory and vestibular function and the mildest being delayed malfunction of endolymph resorption resulting in fluctuating hearing loss and/or episodic vertigo.

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Ann Otol Rhinol Laryngol 99:1990

ARACHNOID GRANULATION CEREBROSPINAL FLUID OTORRHEA

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A case report and review of the temporal bone (TB) collection in the Department of Otolaryngology at SUNY Health Science Center in Syracuse demonstrated the occurrence of arachnoid granulations (AGs) in the posterior fossa surface of the TB and their role in cerebrospinal fluid (CSF) otorrhea. A large AG responsible for CSF otorrhea in a 64-year-old man was excised with soft tissue repair of the dural defect. Sixteen of 188 TBs (8.5%) in the collection contained 24 AGs ranging in size from 0.07 to 80.65 mm³. Nine AGs (37%) were small (< 1 mm³) and did not demonstrate enlargement. Twelve (50%) were of intermediate size (2.50 to 9.32 mm³), and three (13%) were large (49.82 to 80.65 mm³). The intermediate and large AGs were associated with bone erosion and a high incidence of communication with a pneumatized mastoid complex (serous otitis media or meningitis). These findings suggest that AGs of sufficient size to produce bone erosion are the primary responsible lesions in adult-onset spontaneous CSF otorrhea.

KEY WORDS — arachnoid granulations, cerebrospinal fluid, otorrhea.

INTRODUCTION

Cerebrospinal fluid (CSF) otorrhea is clinically divided into two major categories. Direct and indirect trauma to the temporal bone (TB) (fracture and surgical procedures) is responsible for most cases of CSF drainage. Spontaneous CSF otorrhea is much less common and may occur in both the pediatric and adult age groups.[1,2] Although the cause of a CSF leak from trauma is usually obvious, the pathway for spontaneous CSF drainage is frequently obscure. This obscurity may be responsible for a delay in diagnosis and treatment. Spontaneous CSF otorrhea in the pediatric age group may be a manifestation of congenital patency of a preformed pathway around the otic capsule[3] or a congenital malformation of the labyrinth allowing spinal fluid to flow from the internal auditory canal to the oval or round window.[4-16] Adult-onset spontaneous CSF otorrhea has been attributed to a herniation of brain tissue (encephalocele),[4-11,17-24] meninges (meningocele),[25] both meninges and brain (meningoencephalocele),[26,27] or a dural defect (fistula).[2,28-33] Dural defects in the middle fossa associated with bony defects in the tegmen tympani are the usual location of these spinal fluid leaks, but similar herniations of tissue through dural defects of the posterior fossa mastoid plate have been recorded.[30,31]

The present report contends that the tissue herniations and dural defects responsible for adult-onset spontaneous CSF otorrhea represent aberrant arachnoid granulations (AGs) located in the dural surfaces of the TB. Progressive enlargement of these structures with increased age and intermittent spinal fluid pressure are responsible for bone erosion of the adjacent mastoid cell partitions, leading to communication of the CSF space with the air cell system. This hypothesis is supported by a case report and a review of the TB collection at the Health Science Center in Syracuse.

CASE REPORT

A 64-year-old man presented on April 25, 1989, with a 10-month history of right-sided blockage and hearing loss. A conductive hearing loss in the right ear was treated with decongestants and antibiotics for 2 weeks, followed by a myringotomy and placement of a ventilating tube. The remainder of the otolaryngologic examination revealed normal findings. When the ventilating tube was expelled, a larger-gauge ventilating tube was inserted. The conductive hearing loss persisted and was temporarily improved after a gush of clear watery fluid from the ventilating tube. A computed tomographic scan demonstrated an osteolytic lesion in the posterior fossa plate of the right TB with opacification of the air cell system (Fig 1A). A magnetic resonance imaging scan demonstrated that there was continuity of spinal fluid through the area of bone erosion into the mastoid air cells (Fig 1B). An audiogram demonstrated a symmetric bilateral descending sensorineural hearing loss (20 dB speech reception threshold, 80% speech discrimination) with a small conductive component in the right ear. The preoperative impression was of a large AG causing extensive bone erosion of the right posterior fossa mastoid cortex with a low-pressure intermittent CSF leak. On June 19, 1989, repair of the CSF leak was accomplished through a simple mastoidectomy approach that provided excellent exposure of a polypoid cystic mass enclosed in a fibrous membrane in the posterior fossa plate anterior to the sigmoid sinus (Fig 1C). After removal of the cystic mass from the 10 x 10-mm osseous cavity, a 3 x 4-mm dural defect was found. The mastoidectomy cavity was obliterated with a free adipose tissue graft harvested from the anterior abdominal wall. Histologic examination of a polypoid component of the specimen revealed an architecture compatible with AG (Fig 1D,E). A core of stromal arachnoid cells sepa-

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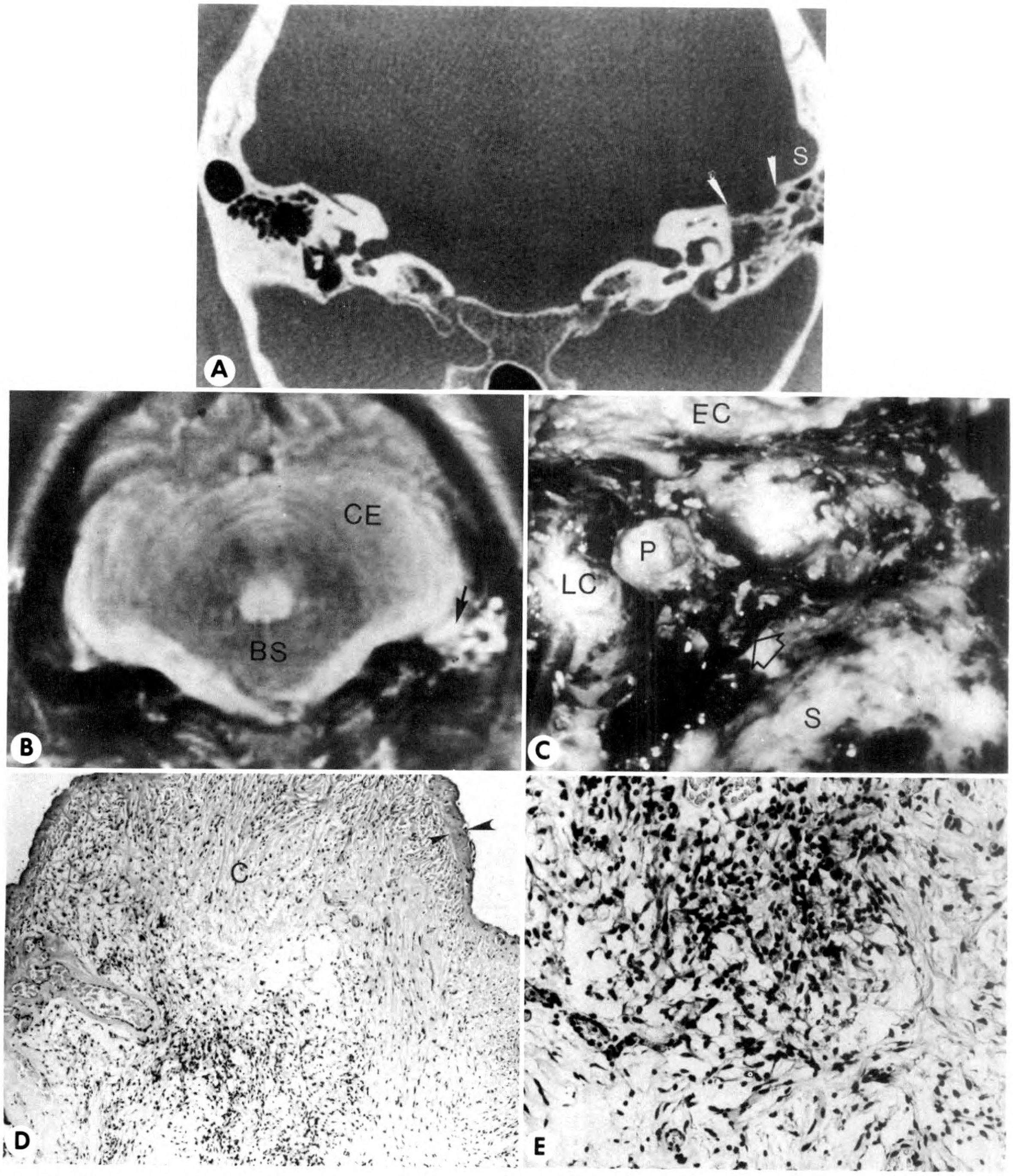

Fig 1. (Patient 1, Case Report.) A) Computed tomogram demonstrating large osteolytic defect (arrowheads) in right posterior fossa mastoid cortex and opacification of air cell system. S — sigmoid sinus. B) T2-weighted magnetic resonance image showing continuity of cerebrospinal fluid from posterior fossa into cystic arachnoid granulation (arrow) and mastoid air cell system. BS — brain stem, CE — cerebellum. C) Surgical exposure of polypoid component (P) of arachnoid granulation in right simple mastoidectomy. Arrow points to margin of bone defect shown in A. S — sigmoid sinus plate, EC — posterior wall of external ear canal, LC — lateral canal prominence. D) Low-power view of polypoid arachnoid granulation shown in C (original x80). Central core (C) is composed of clear spaces separated by collagenous trabeculae and nucleated arachnoid cells enclosed in fibrous covering (arrowheads). E) Higher-power view of central core demonstrating tubular spaces filled with cerebrospinal fluid (center and lower left) while other spaces are collapsed (upper right) (original x200). Spindle and stellate arachnoid cells separate spaces.

rated the fluid-filled spaces and collagen trabeculae in the center of the villus, which was enclosed by a fibrous capsule.

REVIEW OF TEMPORAL BONE COLLECTION

The TB collection in the Department of Otolaryngology at the Health Science Center was reviewed for the presence of AGs. Since most of the TBs were sectioned in a horizontal plane, it was not possible to evaluate the tegmen tympani for the presence of AGs in the middle fossa. Therefore, the study was restricted to AGs occurring on the poste-

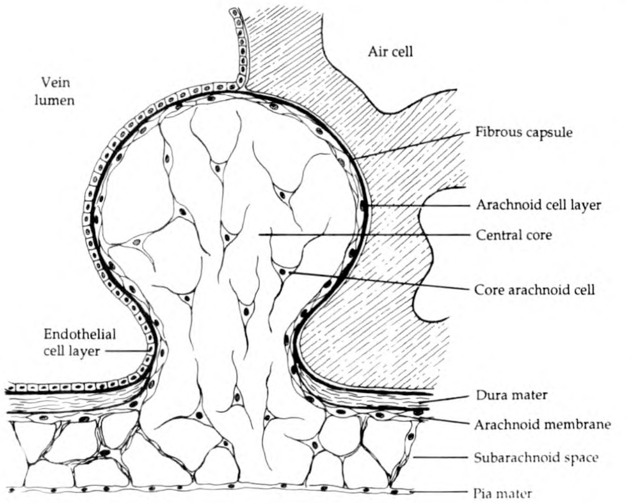

Fig 2. Drawing illustrating components of arachnoid granulation as it occurs in venous sinus (left) and in bone (right).

rior fossa surface of the TB.

Arachnoid granulations are herniations of arachnoidal tissue through a dural defect into the lumen of a venous sinus (Fig 2). The central core of an AG is composed of stellate-shaped arachnoid cells with intervening tubular spaces running longitudinally in the herniated tissue. The core is filled with CSF and covered by a herniated layer of arachnoid cells loosely attached to a fibrous capsule derived from dura and connective tissue. The capsule of the AG that projects into the venous sinus may be partially covered by endothelial cells derived from the intimal surface of the sinus. Since CSF pressure is higher than venous pressure,[34,35] CSF from the subarachnoid space percolates under pressure through the tubular spaces of the arachnoid core to the covering membrane. Spinal fluid crosses the covering layer by pinocytosis and through gaps between the endothelial cells of the cap.[36] Increased spinal fluid pressure forces more CSF through the AG and the endothelial cap into the lumen of the venous sinus, completing the process of CSF resorption.

The AGs found in the TB are modified, in that the endothelial layer covering the AG is absent because the AG does not protrude into the lumen of the venous sinus. Instead, the arachnoid herniation containing CSF is restricted by the fibrous capsule, connective tissue, and bone. The spinal fluid that is transmitted through the stromal core of the AG is trapped in the AG and may produce some erosion from the pulsed pressure of the subarachnoid space.[1]

Two criteria were used for the identification of AG in the human TB.

1. The presence of an arachnoid tissue herniation with a surrounding space enclosed in a fibrous capsule within a bony defect in the posterior fossa wall of the mastoid compartment (Fig 3). The space is an artifact produced by postmortem retraction of the core from the fibrous layer. This retraction is a result of a marked drop in subarachnoid space pressure and fixation. Arachnoid cell clusters embedded within the dural layers were not included in this study.

2. A bony defect in the posterior fossa plate with a cystic space lined by a fibrous membrane, often filled with red blood cells, and a proteinaceous precipitate, but lacking the stromal core of the AG (Fig 4). Psammoma bodies characteristic of arachnoidal tissue were sometimes embedded in the connective tissue components of the fibrous capsule. Arachnoid granulations avulsed from the TB during brain removal separate at the tenuous attachment to the capsule. Such avulsions probably are responsible for underrecognition of AGs.

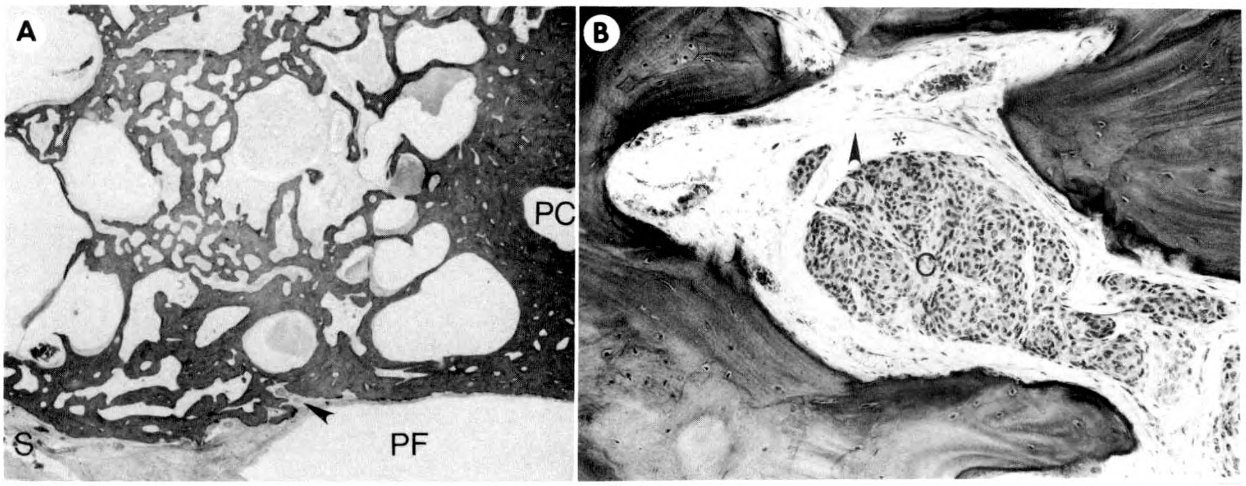

Fig 3. (Patient 15) A) Low-power view of temporal bone with small arachnoid granulation (arrowhead) (original x10). Small amount of fluid in air cells is agonal. S — sigmoid sinus, PF — posterior fossa, PC — posterior semicircular canal. B) High-power view of small arachnoid granulation in A showing fibrous capsule (arrowhead) separated by artifactual space (asterisk) from central core (C) of arachnoid tissue (original x200). There is no evidence of bone erosion.

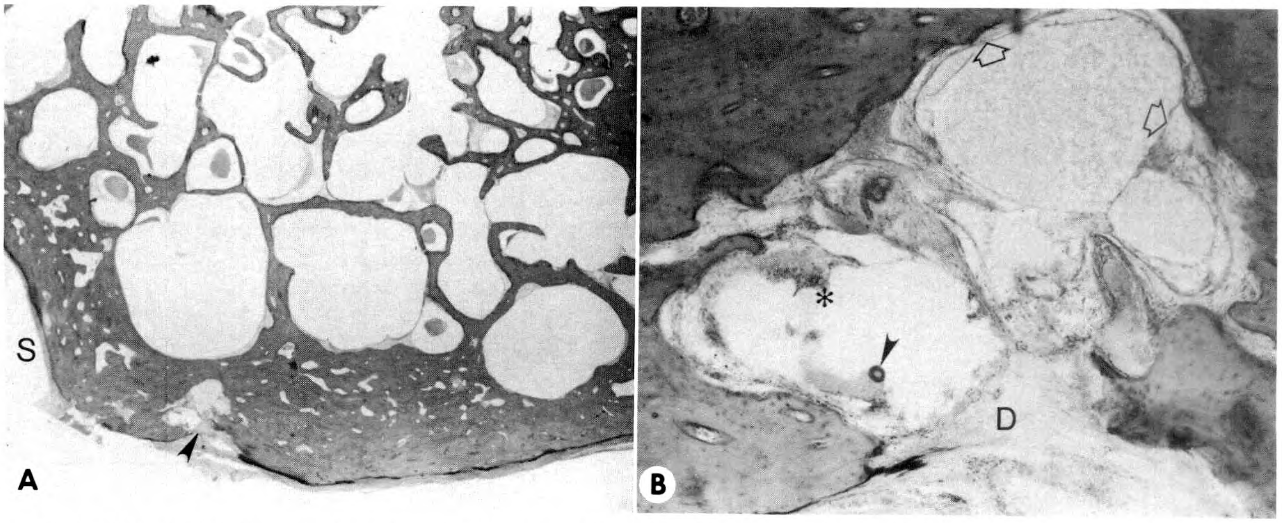

Fig 4. (Patient 11) A) Temporal bone demonstrating bone defect of small avulsed arachnoid granulation (arrowhead) (original x10). Small accumulation of agonal fluid is present. S — sigmoid sinus. B) Higher-power view of avulsed arachnoid granulation defect (original x80). Open arrows point to part of fibrous capsule that encircles space with granular precipitate. In another compartment there are remnants of arachnoid tissue (asterisk) and psammoma body (arrowhead). No bone erosion is present. D — dural sleeve around entrance to bone defect.

RESULTS

One hundred eighty-eight human TBs were examined, and 16 (8.5%) TBs were found to have one or more AGs in the posterior fossa mastoid plate. A total of 24 AGs were found in these 16 TBs. Eleven of the 16 TBs contained a single AG, while 5 of the TBs had multiple AGs. The right and left TBs of patient 6 (see Table) both showed multiple AGs (Fig 5).

The ages of patients with AGs ranged from 52 to 92 years, with all but one being 60 years or older (mean, 74.6 years). There was an 11 to 4 female preponderance. However, it should be noted that age and sex may be influenced by the inherent bias of a TB collection.

The size of the AG was measured with a stereologic point-counting technique based on the Cavalieri principle of assessing volume.[37] A point-counting matrix was used in a macro projector (large AGs) or in a light microscope (intermediate and small AGs) to tabulate points that overlay the AGs in TB sections. The total points representing the area of each AG in a section were used to calculate volume by multiplying the total of AG areas in sections by the distance between sections. Volume was calculated in cubic millimeters so that clinical comparisons could be made. The fibrous capsule surrounding the arachnoid core was used as the outer limit of the AG for these measurements.

The Table summarizes the size of AGs and pertinent associated findings in these TBs. Three groups of AGs based on size were present: small, intermediate, and large. There were six TBs with nine small AGs that measured less than 1 mm^3. None of these small AGs were associated with erosion of surrounding bone or pathologic findings in the mastoid complex. Twelve intermediate-size AGs measuring between 2 and 10 mm^3 were found in seven TBs. All but one of these were associated with bone erosion from the AG. Four of the seven TBs with intermediate-size AGs were associated with nonsuppurative effusion in the mastoid cell system; one TB (patient 5) showed subarachnoid space infection (menin-

POSTERIOR FOSSA TEMPORAL BONE ARACHNOID GRANULATION

*Patient**	*Age (yr)*	*Sex*	*Size (mm^3)*	*Bone Erosion*	*Other Associated Findings*
2	60	M	78.96	+	Serous otitis media
3	85	F	80.65	+	None
4	81	M	49.82	+	Otitis media, meningitis
5	60	M	9.32	+	Meningitis
			2.90	+	
			2.41	+	
6	80	F (L)	6.96	+	Serous otitis media
			4.93	+	
			2.23	+	
		(R)	4.93	+	
			5.27	+	
7	81	F	6.28	+	Serous otitis media
8	60	F	5.81	+	None
9	81	F	3.52	+	Serous otitis media
10	90	F	2.50	–	None
11	92	F	0.43	–	None
12	82	F	0.41	–	None
13	66	F	0.35	–	None
14	52	F	0.31	–	None
			0.18	–	
			0.18	–	
15	78	M	0.27	–	None
			0.07	–	
16	71	F	0.18	–	None

*Patient 1 is described in Case Report.

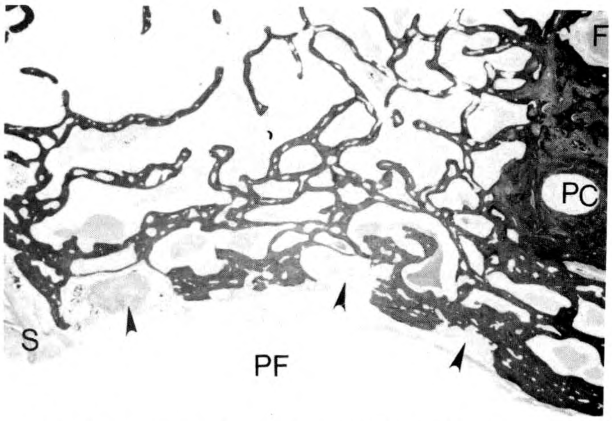

Fig 5. (Patient 6) View of temporal bone showing three arachnoid granulations (arrowheads) associated with early bone erosion and large amount of fluid in mastoid air cells (original x10). S — sigmoid sinus, PF — posterior fossa, PC — posterior semicircular canal, F — facial nerve.

gitis) without evidence of infection in the mastoid system. However, it demonstrated that an intermediate-size AG can reach an extensive air cell compartment after limited bone erosion (Fig 6).

The large AGs were fewest in number (three TBs) and measured from 49.82 to 80.65 mm^3 in size. All three TBs showed extensive erosion of bone; one TB contained serous fluid in the mastoid air cells, while another demonstrated meningitis secondary to acute suppurative otitis media (Fig 7). The large AGs in patients 1 and 2 consisted of large cystic cavities lined by flattened arachnoid tissue and a thin fibrous capsule (Fig 8) with smaller polypoid solid compartments. The third TB (patient 3) contained the largest AG, but neither serous otitis media nor meningitis, because the AG was not located near a mastoid air cell (Fig 9).

DISCUSSION

Arachnoid villi and AGs provide the primary mechanism for CSF resorption into the intracranial venous system.[38] Arachnoid villi first appear in the walls of the major venous sinuses along with formation of the subarachnoid space at the gestational age of 30 weeks. As these villi enlarge with age they form AGs that are recognizable at 36 weeks.[39] They continue to increase in size and complexity with increased age and subarachnoid pressure.[39] The arachnoidal core of AGs is capped by a fibrous capsule derived from dura mater and an endothelial cell layer derived from the intimal lining of the vein.

The structure of the arachnoid core has been studied in detail with both transmission and scanning electron microscopy.[40-45] An accurate description of the AG has been enhanced by the use of in vivo fixation with careful maintenance of normal or increased CSF pressure and meticulous dissection of AGs with surrounding vein wall. These anatomic studies demonstrate a core of columnar spaces separated and covered by stellate arachnoid cells that is covered by the fibrous and endothelial cell membrane.[45,46] The use of tracers and red blood cells in the CSF has permitted a reconstruction of the route of CSF flow through the AG.[46,47] The CSF is pushed under pressure through the tubular channels of the AG filling the central core. Filtration of the CSF through the fibrous and endothelial cell layer into the venous lumen occurs by micropinocytosis and between the overlapping surfaces of adjacent endothelial cells.[36] During increased subarachnoid pressure, widening of these gaps allows for passage of larger volumes of CSF.[36] Although functional AGs of the venous sinuses increase in size and complexity with age,[39] cystic transformation has not been reported, probably because of unobstructed flow of CSF through the core.

Although the majority of AGs are located along

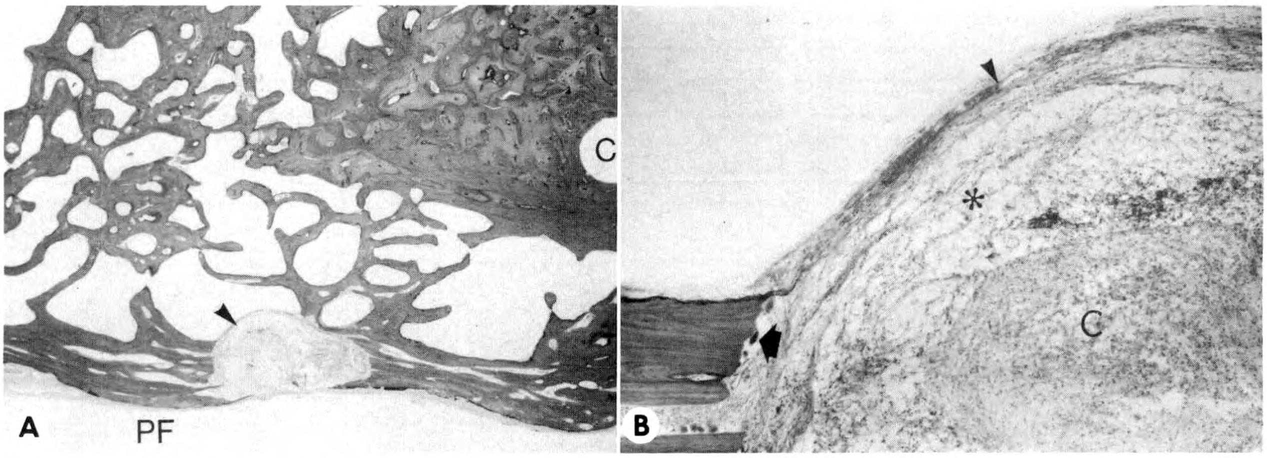

Fig 6. (Patient 5) C — crus commune. A) Temporal bone from 60-year-old man who died after 4-week history of cryptococcal meningitis with hearing loss caused by labyrinthitis (original x10). Intermediate-size arachnoid granulation (arrowhead) has produced bone erosion and protrudes into normal air cell system. B) High-power view of arachnoid granulation in A demonstrating inflammatory infiltrate with cryptococcal organisms in subdural space (asterisk) and separation of arachnoid granulation core from fibrous capsule, which is distended against mucoperiosteum (arrowhead) of air cell (original x200). Large arrow — osteoclasts at edge of bone erosion.

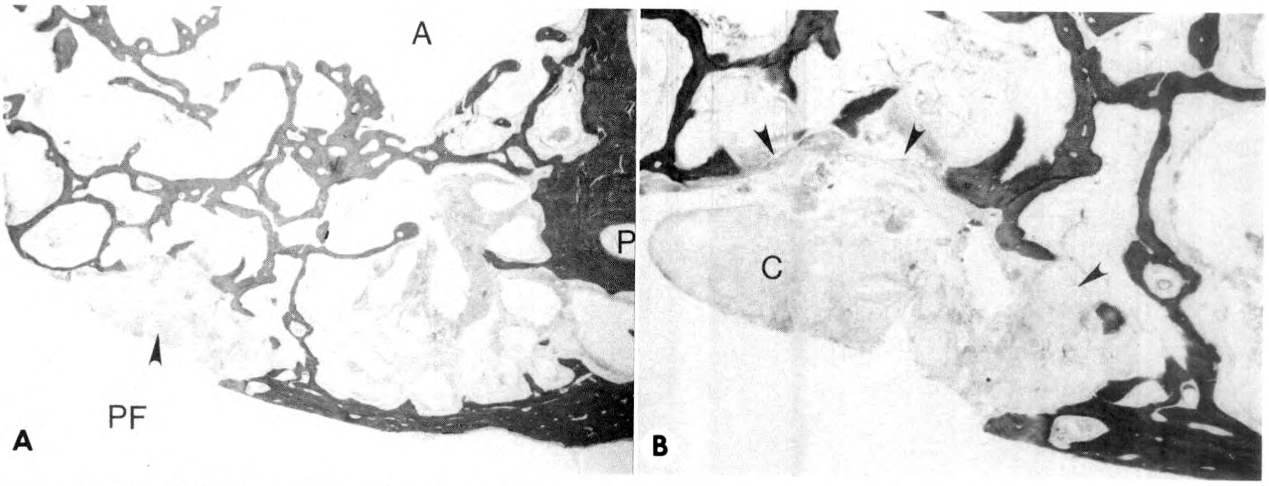

Fig 7. (Patient 4) A) Temporal bone from 81-year-old man who died of pneumococcal meningitis secondary to acute otitis media (original x10). There is continuity of inflammatory cells from mastoid air cells to arachnoid granulation (arrowhead) through several areas of bone erosion. PF — posterior fossa, P — posterior semicircular canal, A — mastoid antrum. B) Higher-power view of arachnoid granulation core (C) and multiple pathways through eroded bone trabeculae (arrowheads) for extension of acute inflammatory process (original x80).

the superior sagittal sinus and its tributaries, they may also be found at other locations in the skull base.[48] These locations include the roof of the sphenoid and ethmoid sinus cells in the anterior cranial fossa, along the eustachian tube and the tegmen tympani of the TB in the middle fossa. Schuknecht and Gulya[49] have called attention to these structures in the middle fossa and posterior fossa surfaces of the temporal bone, particularly as they may be encountered by the otologic surgeon. The location of AGs in the posterior fossa aspect of the TB between the labyrinth capsule and the sigmoid sinus is described in this study. The formation of AGs in this location may represent an aborted attempt to reach and invade the sigmoid sinus in order to resorb CSF. Early encapsulation by ossifying mesenchyme could be a factor in the isolation of AGs within bone defects of the posterior fossa mastoid cortex. Since these AGs do not extend into a venous sinus lumen, they are not covered by an endothelial cell layer, but only by the fibrous capsule that represents an extension of the dura and compressed connective tissue. This closed system of CSF in the AG creates an environment in which the pressure of pulsations in the subarachnoid space is transmitted through the core to cause destruction of the surrounding periosteal bone. A similar mechanism has been proposed to explain the erosion of the stapes footplate in pediatric-onset CSF otorrhea in which the subarachnoid space extends into a congenitally large vestibule (Mondini dysplasia).[1] The extensive cystic component in some large AGs of the TB (Figs 1A and 8) may also represent the cumulative effects of CSF under pressure. Depending on the size and location of the AG as well as the pneumatization of the mastoid compartment, an opportunity exists for extension of the AG into the air cell system. Continued expansion of the AG may result in a low-pressure CSF leak or an opportunity for infection from suppurative otitis media to ascend into the subarachnoid space.

This study demonstrated an 8.5% incidence of AG in the posterior fossa of TBs. Of course, this figure is subject to the bias present in human TB collection (age, cause of death). Ferguson et al[2] observed a 22% incidence of "pit holes" in the middle fossa surface of whole dried TB specimens, confirming the 21% incidence of tegmen tympani defects reported by Ahren and Thulin.[50] These may represent the location of AG in the middle fossa. Arachnoid granulations in the TB often go undetected in postmortem examination, because the arachnoid cell core is commonly avulsed from its TB defect during brain removal. However, indirect evidence of AG presence can be used to recognize these structures, as pointed out in this study. This consists of a

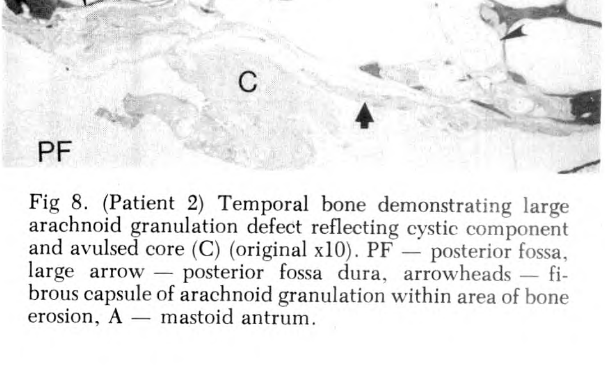

Fig 8. (Patient 2) Temporal bone demonstrating large arachnoid granulation defect reflecting cystic component and avulsed core (C) (original x10). PF — posterior fossa, large arrow — posterior fossa dura, arrowheads — fibrous capsule of arachnoid granulation within area of bone erosion, A — mastoid antrum.

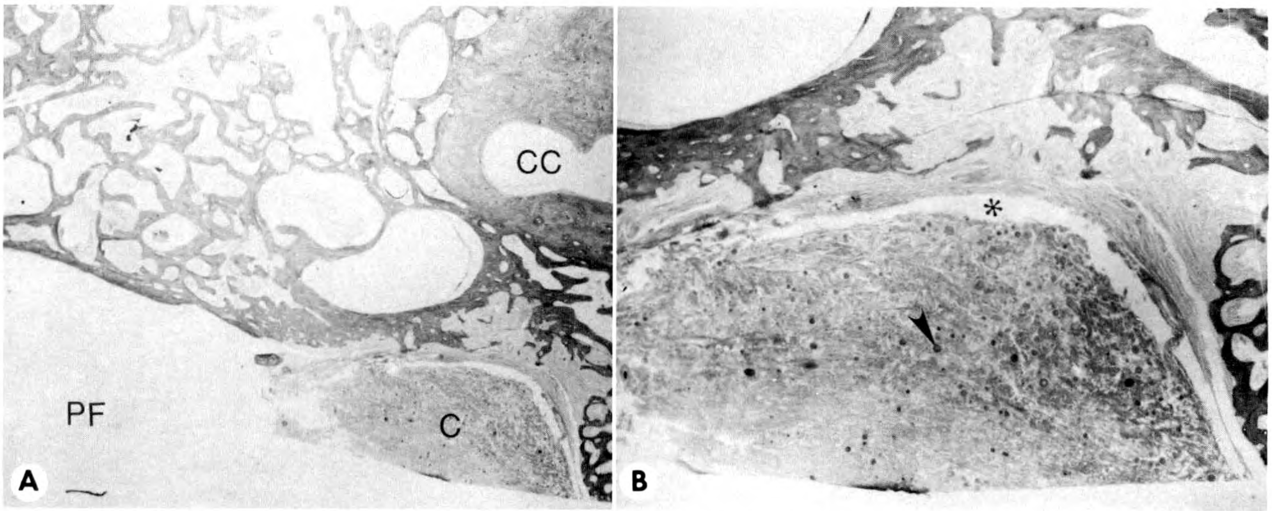

Fig 9. (Patient 3) A) Temporal bone showing large arachnoid granulation core (C) demonstrating bone erosion that has not produced communication with mastoid air cell system because of its medial position (original x10). PF — posterior fossa, CC — crus commune. B) High-power view of arachnoid granulation in A demonstrating psammoma bodies (arrowhead) and separation from fibrous covering (asterisk) (original x80).

bone and dural defect in the posterior fossa mastoid cortex, within which is located a multilocular space lined by a fibrous capsule and connective tissue (Fig 4). Psammoma bodies may be embedded in the connective tissue, which is partly derived from the arachnoid layer.

Three groups of AGs according to size were observed in this study. Small AGs (<1 mm^3) comprised about 37% of the total group and were not associated with bone erosion; these are of no clinical significance. The intermediate AG category (2.50 to 9.32 mm^3) made up 50% of the total, while those in the large category (49.82 to 80.65 mm^3) represented 13% of the total number of AGs in this study. All but 1 of the 15 AGs in these latter two groups were associated with bone destruction, and all but 3 were associated with findings that indicated communication with the mastoid air cell complex. This was represented by a serous effusion within the middle ear and mastoid compartments or suppuration (meningitis) of the AG with or without adjacent suppurative otitis media. Extension of acute suppurative mastoid disease into the subarachnoid space via AGs has been suggested by Schuknecht and Montandon.[51]

The possibility that some of the large AGs represent a coalescence of enlarging multiple smaller AGs is supported by the absence of a continuum of size between 9.32 and 49.82 mm^3. The proximity of progressive bone defects in the TB specimens with multiple AGs (Fig 5) further suggests this possibility. The large AG lesion in our case report is an example of a complex AG that may have been formed by this process. However, large AGs may occur singly, as in patient 3 (Fig 9).

Reports of the surgical findings in adult patients with spontaneous CSF otorrhea have described polypoid tissue associated with the dural defect or a dural defect alone (fistula).[1,4,11,17-22,24,28,29,32,33] Most of these have been located in the tegmen tympani or tegmen mastoidea.[17-20,52] A few have reported the site of CSF leak to be located anterior to the sigmoid sinus on the posterior fossa side.[30,31] Histologic examination of such surgical specimens usually reveals granulation tissue or tissue suggestive of neural elements, because the fluid-filled spaces in the tissue core are collapsed when the CSF is allowed to seep out during excision and fixation, leaving an aggregate of arachnoid cells.

The evidence presented in this study supports the contention that the structure responsible for adult-onset spontaneous CSF otorrhea is AG with bone erosion into the mastoid cell complex. These patients usually present clinically with a serous otitis media or meningitis following acute otitis media.[2] However, the dural defect through which AGs herniate may also be a preformed pathway responsible for intracranial extension of chronic suppurative mastoid disease. An intact dural covering of the TB represents a substantial barrier to extension of infection or neoplasm. The effectiveness of this barrier is evident when a large cholesteatoma or extensive malignancy of the middle ear and mastoid erodes bone of the tegmen or posterior fossa mastoid plate but is contained extradurally.

Hicks et al[12] described 11 patients who presented with CSF otorrhea associated with chronic suppurative middle ear and mastoid disease. A bone and dural defect of 3 mm to 1 cm was responsible for the CSF leak in all 11 patients; 10 defects were located in the tegmen, and 1 in the posterior fossa plate near the sigmoid sinus. Seven of the tegmen defects were associated with a temporal lobe abscess, and 3 were filled with granulation tissue, while the posterior fossa defect was responsible for a lethal cerebellar abscess. Surgical manipulation of soft tissue in all of the dural defects was associated with increased flow of CSF. Repair of the defect with fascia (with and without Marlex mesh) controlled the CSF leak in all 10 cases of attempted repair.

Our interpretation of these observations is that a dural defect responsible for the CSF leak predisposed to the development of intracranial extension of inflammatory disease, including the extension of cholesteatoma matrix into the middle fossa and posterior fossa. Since dural defects are associated with AGs in the middle fossa (22%) surface and the posterior fossa (8.5%) surface of the TB, it is reasonable to assume that AGs may be responsible for intracranial spread of chronic middle ear disease in some patients.[53,54] Similarly, spontaneous adult CSF rhinorrhea may be caused by expansion of AG into ethmoid and sphenoid sinus air cells.[55]

A high level of awareness is needed to recognize this lesion when one is confronted with refractory serous otitis media, otorhinorrhea, or meningitis in an adult. Arachnoid granulations of the TB should be suspected and a careful search carried out with imaging studies. Fine cuts (1 mm) with computed tomographic scanning are capable of revealing the bone defects associated with intermediate and large AGs. Since AGs may invade the mastoid air cell system from the middle fossa or posterior fossa surface, it is necessary to scan the TB in both coronal and transverse planes in order to completely visualize these two surfaces of the TB.

Demonstration of the site of leak may be achieved by two imaging methods. 1) Magnetic resonance imaging is a useful noninvasive study capable of confirming the continuity of the leak from the subarachnoid space into the mastoid air cell compartment and detecting herniation of brain tissue as a cause of the CSF leak. 2) Computed tomographic scanning following intrathecal instillation of metrizamide is an effective invasive technique for isolating the dural defect. If neither technique is able to successfully demonstrate the site of leak, surgical exploration of the mastoid aspect of the middle fossa and posterior fossa dura as recommended by Schuknecht et al[31] is an efficient diagnostic and therapeutic maneuver, aided by the use of preoperative intrathecal injection of fluorescein.

The surgical repair is dependent on the number, size, and location of the AGs. Since labyrinth function is usually normal in adult-onset CSF otorrhea,[1,2] the surgical approach should allow preservation of the sound transmission system. If the preoperative radiographic examination indicates multiple or large (> 1 cm) defects in the tegmen, a middle fossa craniotomy[56] affords the optimal opportunity for exposure and repair (fascia) of the dural defect(s). A small (< 1 cm) solitary leak or an unidentified leak in the tegmen can be managed through an intact canal wall mastoidectomy using a Silastic sheet to support a fascia graft over the dural defect. Dural defects of any size or number in the posterior fossa mastoid surface are effectively repaired by free adipose autograft tissue obliteration of the intact canal wall mastoidectomy defect.

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Ann Otol Rhinol Laryngol 99:1990

NERVE FIBER ANALYSIS AND THE AGING PROCESS OF THE VESTIBULOCOCHLEAR NERVE

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Nerve fiber analyses were performed on the human vestibulocochlear nerve stained with Luxol fast blue–periodic acid–Schiff–hematoxylin with use of a combination of an image-analyzer and a computer. The axons were counted and their transverse (cross-sectional) areas were measured in 12 individuals. The average numbers of axons in each vestibular and cochlear nerve were 17,727 and 25,098, and the average transverse areas of their axons were 4.02 and 1.79 μm^2, respectively. Amyloid bodies and intervening Schwann cells in the vestibulocochlear nerve were also counted. The average number of amyloid bodies was 246 per transverse section of the nerve and their average size was 114 μm^2. The average number of intervening Schwann cells was 1,513. Our results indicated that the transverse axonal areas of the cochlear nerve became reduced with age, while the transverse areas of the amyloid bodies in the vestibulocochlear nerve increased with age. The number of vestibular nerve fibers did not seem to change with age.

KEY WORDS — aging, eighth cranial nerve, Luxol fast blue–periodic acid–Schiff–hematoxylin, nerve fiber analysis, vestibulocochlear nerve.

INTRODUCTION

Craniospinal nerves consist of many individual nerve fibers, most of which are myelinated, while a few are nonmyelinated. These fibers are collected with intervening connective tissue (endoneurium) into nerve fiber bundles (or fasciculi), each of which is enclosed in a connective tissue sheath (perineurium). The nerve fiber bundles gather to form a single nerve that is surrounded by a connective tissue sheath termed the epineurium.

Fiber analyses of the facial or vestibulocochlear nerve may be important for understanding various conditions related to the aging process and diseases, although few data are yet available on this topic.[1-4] The methodology available for analyzing nerves after discrimination of the various histologic components of the peripheral nervous system is quite limited. Components of a nerve to be differentiated include axons, myelin sheaths, connective tissue, neurons, Schwann cells, blood vessels, lipofuscin granules, and amyloid bodies (extracellular hyaline deposits related to aging and stained with Congo red). The authors therefore used a new method[5] to conduct a study of the human vestibulocochlear nerve.

MATERIALS AND METHODS

Human vestibulocochlear nerve trunks and facial nerves with the intermediate nerve were cut off near the brain stem. This material was obtained from corpses for anatomic dissection. The body was placed in a coffin after death with enough dry ice to minimize the postmortem changes until it was put into a cold chamber at 4°C. Twenty-four hours after death, the cadaver was injected with formaldehyde into the arterial system for fixation. The causes of death indicated no direct or indirect connection with the vestibulocochlear nerve, and thus, nerves studied were considered normal. One nerve was collected from a 24-year-old individual, and two nerves from each of two individuals from the 5th to 10th decades of life.

Regarding the methodology, the same procedure as in our recent report[6] was employed. After fixation of the nerves in formaldehyde (3.7%) followed by secondary fixation[5] with a mixed solution of 5% potassium dichromate and 5% potassium chromate (1:4, volume/volume), the blocks were embedded in celloidin and were sectioned transversely into 10- or 20-μm thick slices and stained with Luxol fast blue–periodic acid–Schiff–hematoxylin (LPH).[5] The shrinkage of the nerve tissue sections during fixation and embedding amounted to approximately 10% in length.

For the measurement and analysis of the vestibulocochlear nerve fibers, a combination of a microscope, drawing tube (or camera lucida), electronic optical planimeter (Digiplan, Kontron Co), and computer (PC-9801VX2, NEC) was adopted. Enlarged images (50 times) of transverse sections (20 μm thick) of the vestibulocochlear nerves were traced with a diode piloting cursor to measure the transverse areas of the nerve fiber bundle, excluding surrounding and intervening connective tissue. Further enlarged images (134 times) were traced to measure the transverse areas of amyloid bodies and to count the numbers of amyloid bodies and intervening cell nuclei. The borderline between the cochlear and vestibular nerve fiber bundles was determined according to the criteria of Engström and

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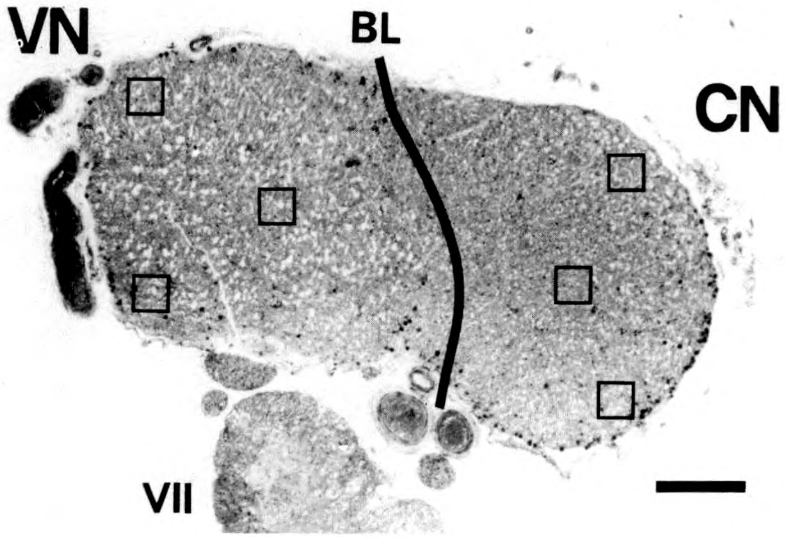

Fig 1. Transverse section of vestibulocochlear and facial (VII) nerve. (Luxol fast blue–periodic acid–Schiff–hematoxylin [LPH]). Squares in vestibular (VN) and cochlear (CN) nerves indicate sampling sites. Three sampling sites of nerves were determined as follows: center of nerve, and two peripheral sites that were located farthest from border (see text) and center. BL — borderline between cochlear and vestibular nerves, bar — 0.3 mm.

Rexed.[7] Highly enlarged images (1,340 times) were used with oil immersion to measure the transverse areas of the axons and to count the numbers of axons. It is rather difficult to clearly decipher the boundary between the axoplasm and the myelin sheath under the light microscope without using an oil immersion objective. For the measurement of the nerve fibers, three sampling sites on each vestibular nerve and cochlear nerve were selected, as shown in Fig 1. Each sampling area covered an area of 0.0030 mm^2. In each nerve, data from the three sampling sites were statistically examined by analysis of variance. The total number of nerve fibers was calculated from the average number of nerve fibers per sampling area and the transverse area of the nerve fiber bundle excluding connective tissue. A regression analysis was performed between numbers of nerve fibers and age, and between axonal areas and age.

RESULTS

The nerve from the 24-year-old individual was sectioned transversely. The axons, however, appeared to be cut slightly obliquely. Thus, this nerve was excluded from the measurement of numbers and sizes (areas) of axons, although it was included in counts of intervening cell nuclei and amyloid bodies, which were spherical in most cases.

NUMBERS OF NERVE FIBERS

Vestibular Nerve. The number of vestibular nerve fibers was estimated to range from 13,996 to 20,760 (average, 17,727). The data for all cases are listed in Table 1. Most of the thick fibers appeared to be myelinated (each with a blue-green myelin sheath surrounding a dark purple or black axon; see Fig 2), and among them there were some thin unmyelinated fibers (Fig 2). Thin unmyelinated fibers were not included in the counts.

TABLE 1. FIBER ANALYSES OF VESTIBULAR NERVE

Case	*Age*	*Sex*	*Total No. of VN Fibers*	*Area of TSs of VN (mm^2)**	*Average Area of Axons in TSs (μm^2)*	*Sum of Axonal Areas per Section (mm^2)*	*Area Ratio of Axons to Nerve Fibers*†	*Circularity Ratio*§
1359R	43	M	20,712	0.575	3.55	0.0734	0.128	0.83
1337L	47	M	16,660	0.598	4.33	0.0721	0.121	0.88
311R	54	M	19,189	0.652	4.74	0.0910	0.140	0.89
97R	57	M	16,013	0.398	3.25	0.0521	0.131	0.88
1336R	66	F	14,087	0.468	5.03	0.0710	0.152	0.89
1349L	69	F	18,855	0.696	4.39	0.0828	0.119	0.83
1344R	76	M	20,324	0.590	3.44	0.0670	0.114	0.83
1332R	77	M	16,845	0.612	4.34	0.0731	0.119	0.89
1347L	85	M	20,760	0.878	3.50	0.0727	0.083	0.90
1361R	85	F	13,996	0.481	4.01	0.0561	0.117	0.87
1354L	92	F	15,468	0.603	2.88	0.0445	0.074	0.88
1355L	93	F	19,815	1.034	4.75	0.0948	0.092	0.90
Average			17,727	0.632	4.02	0.0709	0.116	0.87

VN — vestibular nerve, TSs — transverse sections, R — right, L — left.

*Without connective tissue.

†Ratio of column 7 to column 5.

§See text for description.

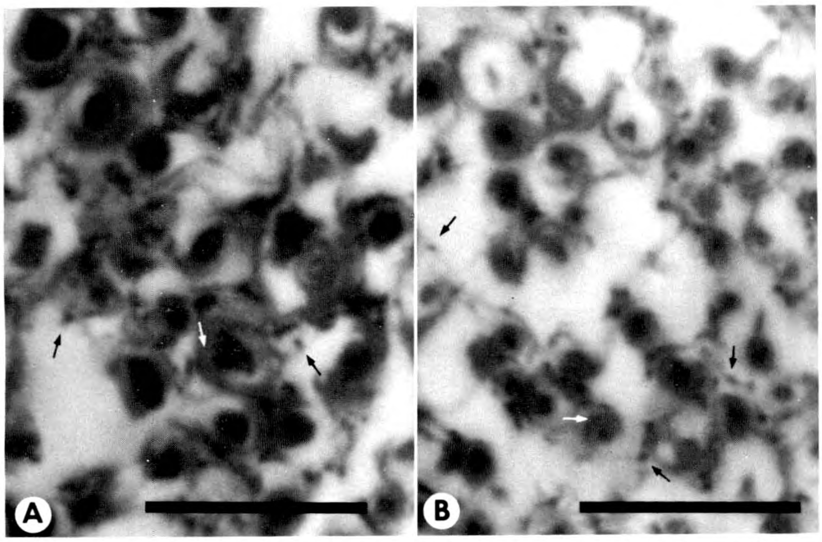

Fig 2. High-power views of nerves (oil immersion; LPH). Black arrows — unmyelinated fibers, white arrows —myelin sheath surrounding axon, bar — 20 μm. A) Vestibular nerve. B) Cochlear nerve.

Cochlear Nerve. The numbers of cochlear nerve fibers ranged from 18,140 to 35,110 (average, 25,098). The data for all cases are listed in Table 2. Most of the thick fibers again appeared to be myelinated (each with a blue-green myelin sheath surrounding a dark purple or black axon; see Fig 2) with the intervention of very thin unmyelinated fibers that were more frequently observed than in the vestibular nerve.

According to our analysis of the vestibular and cochlear nerve fibers, there were no significant differences in numbers and areas of fibers among the three sampling sites in each nerve. The numbers of nerve fibers in the vestibular and cochlear nerves did not seem to decrease with age (vestibular nerve: $r = -.10$, $p > .1$; cochlear nerve: $r = -.28$, $p > .1$).

SIZES OF NERVE FIBER BUNDLES AND AXONS

Vestibular Nerve. The size of fiber bundles of the vestibular nerve (transverse areas of the vestibular nerve without connective tissue) ranged from 0.398 mm^2 to 1.034 mm^2 (average, 0.632 mm^2). The transverse areas of axons ranged from 2.88 μm^2 to 5.03 μm^2 (average, 4.02 μm^2). The data for all cases are listed in Table 1. There was no clear difference in the area distribution of the axons among the three sampling sites in each case. Figure 3 illustrates the distribution of the transverse axonal areas. The axonal areas in each case revealed a nearly normal distribution (SD, 1.1 to 1.8) except for those from subjects in their sixties. They showed a slightly wide distribution (SD, 1.7 and 1.8, respectively).

The sum of transverse areas of axons in each case ranged from 0.0445 to 0.0948 mm^2 (average, 0.0709 mm^2), representing from 7.4% to 15.2% (average, 11.6%) of the total transverse area of the vestibular nerve fiber bundles. The average size and sum of axons in the vestibular nerve did not seem to decrease with age ($r = -.14$, $p > .1$; $r = -.15$, $p > .1$).

TABLE 2. FIBER ANALYSES OF COCHLEAR NERVE

Case	*Age*	*Sex*	*Total No. of CN Fibers*	*Area of TSs of CN* (mm^2)*	*Average Area of Axons in TSs* (μm^2)	*Sum of Axonal Areas per Section* (mm^2)	*Area Ratio of Axons to Nerve Fibers*†	*Circularity Ratio*§
1359R	43	M	25,014	0.620	2.24	0.0560	0.090	0.85
1337L	47	M	33,033	0.837	2.04	0.0674	0.081	0.84
311R	54	M	25,668	0.614	2.17	0.0557	0.091	0.86
97R	57	M	20,841	0.441	2.07	0.0431	0.098	0.86
1336R	66	F	32,990	0.863	2.19	0.0713	0.083	0.85
1349L	69	F	19,692	0.476	1.49	0.0293	0.062	0.87
1344R	76	M	24,552	0.517	1.72	0.0422	0.082	0.84
1332R	77	M	20,318	0.505	1.85	0.0376	0.074	0.86
1347L	85	M	24,906	0.714	1.47	0.0366	0.051	0.88
1361R	85	F	35,110	0.724	1.46	0.0513	0.071	0.87
1354L	92	F	18,140	0.565	1.38	0.0250	0.044	0.87
1355L	93	F	20,906	0.716	1.45	0.0303	0.042	0.88
Average			25,098	0.633	1.79	0.0455	0.072	0.86

CN — cochlear nerve, TSs — transverse sections, R — right, L — left.

*Without connective tissue.

†Ratio of column 7 to column 5.

§See text for description.

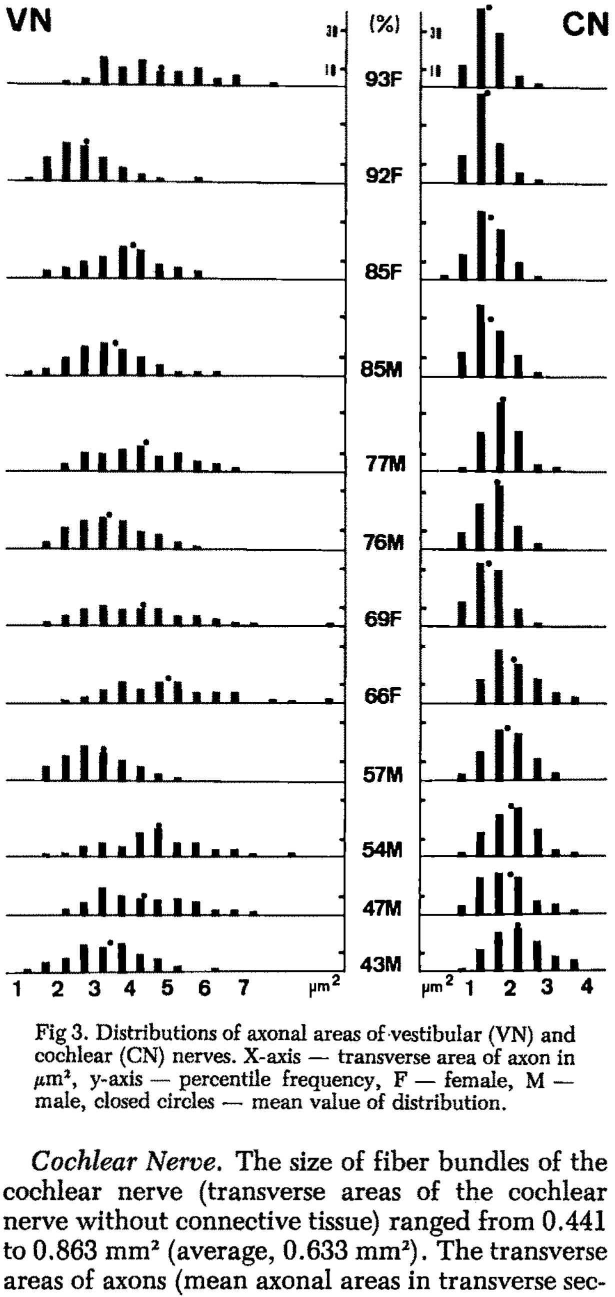

Fig 3. Distributions of axonal areas of vestibular (VN) and cochlear (CN) nerves. X-axis — transverse area of axon in μm^2, y-axis — percentile frequency, F — female, M — male, closed circles — mean value of distribution.

Cochlear Nerve. The size of fiber bundles of the cochlear nerve (transverse areas of the cochlear nerve without connective tissue) ranged from 0.441 to 0.863 mm^2 (average, 0.633 mm^2). The transverse areas of axons (mean axonal areas in transverse section) ranged from 1.38 to 2.24 μm^2 (average, 1.79 μm^2). The data for all cases are listed in Table 2. There was no clear difference of size among the three sampling sites in each case. The distribution of the transverse axonal areas is illustrated in Fig 3. The axonal areas in each case revealed a nearly normal but rather narrow distribution (SD, 0.4 to 0.9). The sum of the transverse axonal areas in each case ranged from 0.0250 to 0.0713 mm^2 (average, 0.0455 mm^2), representing 4.2% to 9.8% (average, 7.2%) of the total transverse area of the cochlear nerve fiber bundles. A scatter diagram and its regression line between the average size of the cochlear nerve axons and age are shown in Fig 4 ($r = -.87$, $p < .01$). The average size and sum of axons of the cochlear nerve fiber bundles decreased with age ($r = -.68$, $p < .01$).

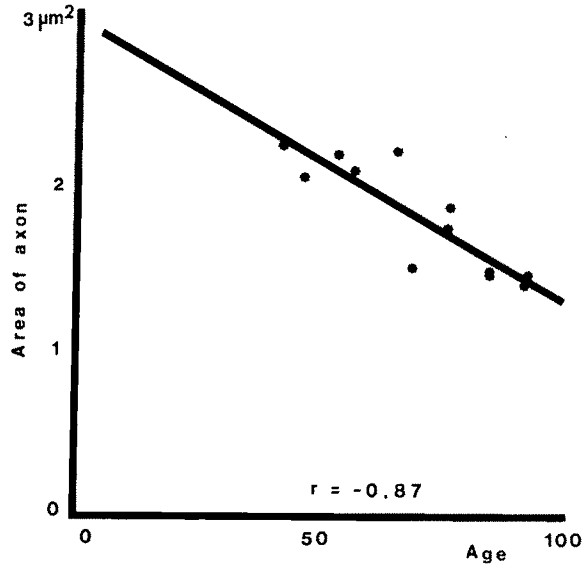

Fig 4. Scatter diagram and regression line between mean transverse area of cochlear nerve axon and age ($p < .01$).

CIRCULARITY RATIO

The circularity ratio (CR) of the axons was calculated as follows:

$$CR = 4\pi \times \text{area (in } mm^2)/(\text{perimeter [in mm]})^2$$

The CR values of the vestibular nerve axons in each case are listed in Table 1. The average CRs for each decade ranged from 0.83 to 0.90 (average, 0.87). The distribution peak of CRs was between 0.9 and 1.0 in every case except for the specimens from subjects 43 and 76 years old. An evaluation of CR values will be discussed later. The CR values of the cochlear nerve axons in each case are listed in Table 2. The average CRs for each decade ranged from 0.84 to 0.88 (average, 0.86). The distribution peak of CRs was between 0.8 and 0.9 in every case. The axonal shapes of both the vestibular and cochlear nerves cut transversely were generally found to be circular or oval (for the most part). In the vestibulocochlear nerve, no axons that were club-shaped, crescent-shaped, or asterisk-shaped were found, while they were sometimes observed in the facial nerve.[6] The mean values of CRs were fairly constant with age. Axons in which the CRs were lower than 0.6 were not present in the vestibulocochlear nerve.

AMYLOID BODIES AND INTERVENING CELL NUCLEI

Amyloid bodies that were stained purple by periodic acid-Schiff (PAS; part of LPH stain) were found in transverse sections of the vestibulocochlear nerve (Fig 5). They were observed in every individual except the 24-year-old. The total number of amyloid bodies per section ranged from 95 to 425 (average, 246) and showed a slight increase with age. The number of intervening cell nuclei that con-

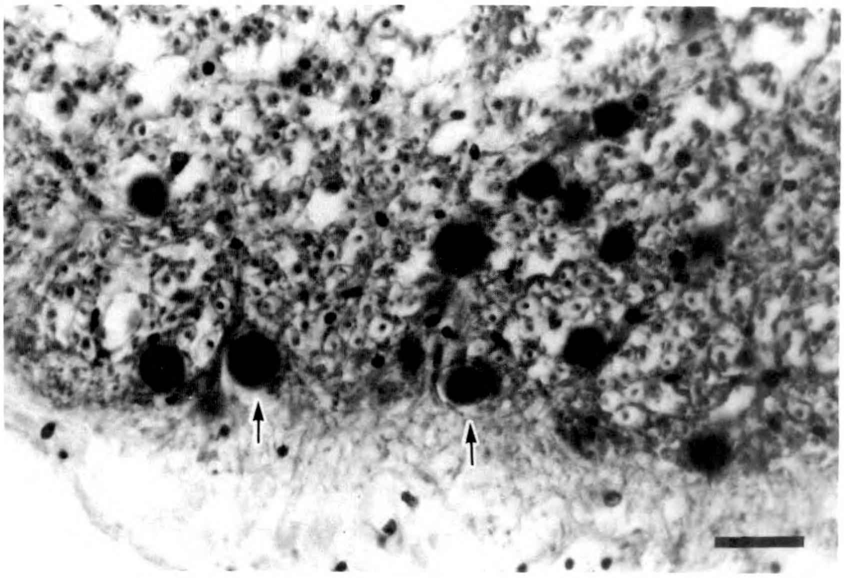

Fig 5. Amyloid bodies (arrows) in vestibular nerve (LPH). Bar — 20 μm.

sisted of Schwann cells and connective tissue cells ranged from 956 to 1,980 (average, 1,513) per single transverse section. The data are summarized in Table 3.

The size of the amyloid bodies (mean areas of amyloid bodies per transverse section) ranged from 74 to 217 μm^2 (average, 114 μm^2). The area distributions of the amyloid bodies are illustrated in Fig 6. Each individual had a rather wide distribution of amyloid body size (SD, 43 to 105). The mean area and the numbers of amyloid bodies that were larger than 200 μm^2 showed an increase with age (area: $r = .76$, $p < .01$; number: $r = .77$, $p < .01$). A scatter diagram and its regression line between the mean area of amyloid bodies and age are given in Fig 7.

DISCUSSION

There are a few reports concerning the normal number of human vestibular nerve fibers.[2,8] According to these reports, the total number of fibers per vestibular nerve ranged from 11,506 to 24,000. Our data (from 13,996 to 20,760; average, 17,727) lie within the above range and are similar to the reported number of vestibular neurons in Scarpa's ganglion (18,439).[9] Bergström[2] studied the vestibular nerves from 11 individuals whose ages ranged from 1 day to 85 years old. She found a correlation between age and the number of vestibular nerve fibers in these individuals and suggested that there was a general reduction in number of vestibular nerve fibers with increasing age, usually beginning at around the age of 40. However, our data did not reveal any decrease in number of vestibular nerve fibers with age. The discrepancy between Bergström's data and ours cannot be explained. It may be related to the small number of samples and differences in counting techniques.

The size of vestibular nerve fibers was determined from measurements of the internal caliber of the myelin sheath by previous authors.[3,7,10,11] The diameters given in the literature[3,7,10,11] were 4 to 9,[3] 2 to 9,[7] 2 to 6,[10] and 5 to 11[11] μm. Bergström[3] found that the caliber of the vestibular nerve fibers in the internal auditory canal near the vestibulum changed with age. The mean caliber was the largest in the adult group (22 to 53 years old), followed by the old group (78 to 85 years old) and the newborn group. Her study is considered to be important for the fiber analysis of the vestibular nerve. However, it is by no means guaranteed that the internal caliber and shape of the myelin sheath actually represent the diameter and shape of the axon. The present authors measured the axonal area itself (3 to 5 μm^2), and the data did not reveal any change with age.

When human autopsy material is used, various sources of error must be taken into consideration in performing histologic morphometry: 1) time and care before autopsy, 2) fixation technique and fixatives, 3) embedding, 4) section thickness, and 5) measuring. Time and care before autopsy (see Materials and Methods) is very important in minimizing the postmortem changes. Postmortem tissue anoxia for extended periods of time may cause shrinkage of plasmalemma. The phenomenon of autolysis may also be accelerated when a cadaver is kept at a high temperature.

Fixation is one of the most important operations in the morphometric analysis. For instance, formaldehyde fixation may cause extreme shrinkage of tissue during histologic processing. In the present study, secondary fixation with chromic acid[5] was employed after the formaldehyde fixation to reduce tissue shrinkage (about 10% in length in three dimensions). We sometimes observed a very thin space between the axon and the myelin sheath in many nerve fibers (Fig 2). This might be due to ax-

TABLE 3. AMYLOID BODIES AND INTERVENING CELL NUCLEI IN VESTIBULOCOCHLEAR NERVE

Case	*Age*	*Sex*	*Total No. of ABs*	*Mean Area of ABs (μm^2)*	*Total Area of ABs ($x10^{-3}$ mm^2)*	*Area Ratio of ABs (Column 6) to VCN*	*No. of ABs >200 μm^2 in Area*	*Total No. of Cell Nuclei**	*Ratio of Column 9 to VCN Area in mm^2*
1333R	24	M	0	0	0	0	0	1,968	631
1359R	43	M	124	74	9.3	0.7	1	1,019	713
1337L	47	M	324	103	33.3	1.7	18	1,579	786
311R	54	M	392	94	36.8	2.1	15	1,133	640
97R	57	M	154	85	13.1	1.3	6	956	928
1336R	66	F	276	80	22.2	1.3	8	1,980	1,200
1349L	69	F	155	104	16.1	1.1	9	1,036	682
1346R	74	F	199	128	25.4	1.7	33	1,731	1,146
1344R	76	M	285	103	29.4	2.2	14	1,696	1,266
1347L	85	M	244	129	31.6	1.6	37	1,772	877
1361R	85	F	284	143	40.7	2.5	69	1,555	966
1354L	92	F	425	110	46.7	2.9	37	1,414	873
1355L	93	F	95	217	20.6	0.9	48	1,833	815
Average			246†	114†	27.1†	1.7†	25†	1,513	960

ABs — amyloid bodies, VCN — vestibulocochlear nerve in transverse sections, R — right, L — left.

*Includes oligodendrocytes, astrocytes, microglia, and connective tissue nuclei.

†Mean value of 12 cases; excludes case 1333R.

on shrinkage and also suggests that the shrinkage ratio might be different between the axon and the myelin sheath. For light microscopy there have been two alternative embedding media, paraffin and celloidin. One of the disadvantages of paraffin is the marked shrinkage of the tissue that occurs during processing. This technique is not suitable for morphometry. The paraffin technique was replaced with celloidin embedding after secondary fixation. An instrumental measurement system always involves some error. An accidental error of the instrument system employed in this study can be less than 1% in area.

As far as the normal number of human cochlear nerve fibers is concerned, there have been several reports.[8,12,13] According to these reports, the total numbers of cochlear nerve fibers ranged from 18,340 to 40,000. Our data (from 18,140 to 35,110; average, 25,098) lie almost within the above range and are similar to the reported number of spiral ganglion cells in Rosenthal's canal (29,024).[14] However, no information on age-related changes of the number of the cochlear nerve fibers could be found in the literature. Our data did not statistically indicate any decrease in the number of cochlear nerve fibers with age.

For the measurement of cochlear nerve fiber size, the same method was employed as for the cochlear nerve.[7,10,11] The diameters (internal caliber of the myelin sheath) of the cochlear nerve fiber reported in the literature[7-9] were 2 to 5,[7] 2 to 4,[8] and 3 to 7[9] μm. These data did not include any age-related findings for the diameter of the cochlear nerve fibers. In our study, the average sizes of the axons in each case were calculated at 1 to 3 μm^2 (1 to 2 μm in diameter) and showed a decrease with age (Fig 4). The differences may be due to those between the internal caliber of myelin sheaths and the axonal diameter.

Using histologic criteria, Schuknecht[15] has classified presbycusis into four types (sensory, neural, strial, and cochlear conductive). Neural presbycusis is due to a loss of neurons in the auditory nerve. Severe loss of spiral ganglion cells near the basal turn of the cochlea in aged patients has been reported by several authors.[15-18] Loss of neurons in the cochlear nuclei has also been verified in aged patients.[19] However, to date there has been no report examining the numeric reduction of the cochlear nerve fibers with age. Our data regarding the decrease in size of cochlear nerve axons related to aging suggest the possible existence of another form of presbycusis. It is, of course, necessary to study morphometric histology of cochlear nerves from individuals with presbycusis.

To evaluate the axonal deformity and parallelism of axonal directions in the vestibulocochlear nerve, the CRs of axons were examined. The average CRs of the vestibular and cochlear nerve fibers were 0.87 and 0.86, respectively. The data indicate that fibers of the vestibulocochlear nerve were nearly circular and seemed to be better arranged than axons of the facial nerve (average CR, 0.79).[6] However, as the facial nerve contains 16% axons with a CR value lower than 0.6, the rest of the facial nerve axons may be closer to a circle.

The human vestibulocochlear anastomosis that bridges the vestibular and cochlear nerves in the internal auditory meatus has been observed in serially sectioned temporal bones.[20,21] It is composed of olivocochlear fibers that represent the efferent nerve supply to the organ of Corti. The fiber population of the anastomosis in humans has been examined by Arnesen.[22] He estimated the presence of two efferent auditory nervous systems, one innervating the outer hair cells and the other innervating the inner hair cells.[23] In the present study, the authors found numerous fine unmyelinated fibers intervening dif-

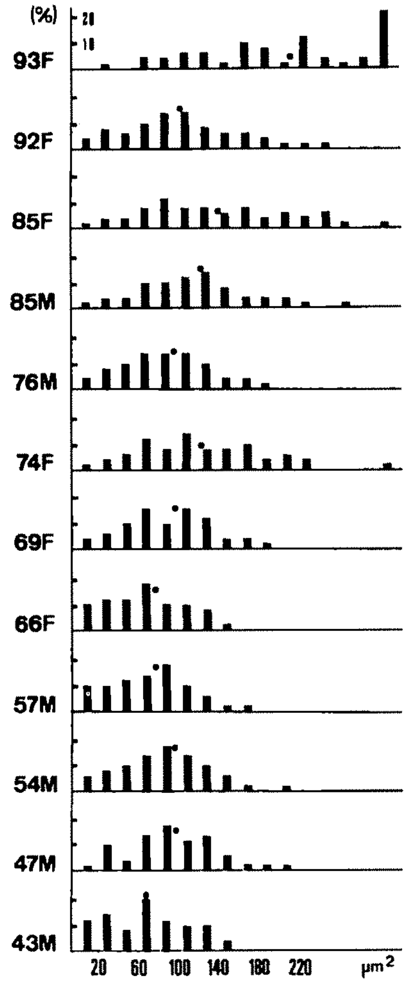

Fig 6. Area distributions of amyloid bodies in transverse sections of vestibulocochlear nerve. X-axis — transverse area of amyloid bodies in μm^2, y-axis — percentile frequency, F — female, M — male, closed circles — mean value of distribution.

fusely among the myelinated fibers of the cochlear nerve. The nature and function of these unmyelinated fibers, however, remain unknown, in spite of Arnesen's data[22] on the olivocochlear fibers, because it used to be difficult to identify unmyelinated fibers with conventional staining methods. No report dealing with the location of the human olivocochlear fibers near the brain stem has yet been published in the literature, insofar as the authors are aware.

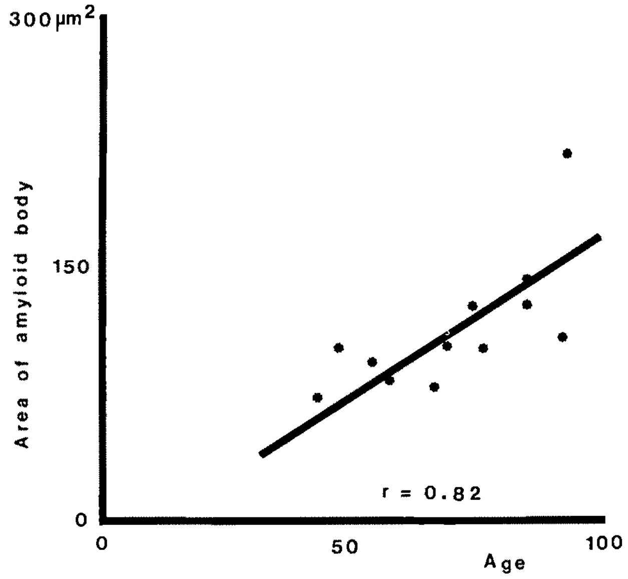

Fig 7. Scatter diagram and regression line between mean amyloid body area of vestibulocochlear nerve and age ($p < .01$).

The obvious presence and an increase in amyloid bodies were verified in the vestibulocochlear nerve by the LPH method.[5] It is considered that amyloid bodies appear in various organs (brain, aorta, heart, pancreas, etc) with age. Moreover, amyloidosis has been mentioned as a cause and manifestation of senile deterioration.[24] The frequency of amyloid body appearance in the above-mentioned organs was found to increase with age from the sixties to the nineties.[25] Recently, amyloid bodies in the central nervous system have been actively investigated histopathologically, biochemically, and immunocytochemically.[26,27] In particular, the discovery that β-amyloid peptide in the cerebral vessels and senile plaques of Alzheimer's disease is encoded by chromosome 21q21 sublocalization of a gene[28] represents a significant step toward explaining the pathogenesis of Alzheimer's disease. The presence of amyloid bodies in the peripheral nervous system of the aged, except for amyloid neuropathy, has not been described in the literature. No morphometric or quantitative analyses of amyloidosis have been published. The present authors found amyloid bodies in the vestibulocochlear nerve of specimens over 40 years of age, mainly in the fibrous marginal regions. The mean area and the number of amyloid bodies that were larger than 200 μm^2 increased with age.

It is of value to study the peripheral nervous system as well as the central nervous system in order to elucidate the aging process. The question arises as to why amyloid bodies have not been found in the peripheral nervous system until now. One reason might be the lack of methods that can discriminate among the different structures in the peripheral nervous system. The LPH stain, one of the discriminative staining methods, was adopted for the present study and permitted every structure (axon, myelin sheath, nucleus, nucleolus, Nissl's bodies, glia, connective tissue, amyloid bodies, lipofuscin granules, vessels, etc) to be easily recognized with only extremely rare artifacts. This method will greatly facilitate morphometric evaluations of the peripheral nervous system because of the clear discrimination of structures (myelin sheath, blue-green; axon, black or dark purple; neuronal nucleolus, dark blue; other cell nuclei, similar findings to conventional hematoxylin stains; connective tissue, faint pink; amyloid body and lipofuscin granule, light purple; etc). Amyloid bodies are abnormal intercellular products considered to be a complex of acid mucopolysaccharides of the chondroitin-sulfuric acid type. They can be amply demonstrated by the iodine reaction, PAS reaction, Congo red, methyl violet, crystal violet, and aniline blue. These methods cannot truly be considered to produce a specific stain because of a false-positive stain for collagen (Congo red), a positive stain for lipofuscin (PAS), and metachromasia for amyloid (methyl violet, crystal violet, aniline blue). However, these methods are valuable at present in demonstrating amyloid bodies. In this study, the PAS reaction was employed as a part of the LPH stain.

Among the facial, vestibular, and cochlear nerves, the mean transverse areas of axons were 6.2, 4.0, and 1.8 μm^2, respectively. No comparative data for these three nerve fibers are available in the literature for excellent methods such as discriminative staining methods. Engström and Rexed[7] measured the caliber of the myelin sheath of both the cochlear nerve and vestibular nerve, but not the facial nerve. Amyloid bodies appeared and increased in the vestibulocochlear nerve with aging, while they were not observed in the facial nerve. The authors have no answer as to why the facial nerve might exclude deposited amyloid bodies, except for the fact that there is a difference in the mean transverse area of the axons and of functions: one is motor, while the other two are sensory. In conclusion, it can be said that the research on the peripheral nervous system adopting a combination of a discriminative staining method, electronic image-analyzer, microscope, and computer should greatly facilitate the elucidation and evaluation of data obtained from peripheral nerve fiber analyses in relation to aging or diseases.

ACKNOWLEDGMENTS — The authors thank Professor H. Tomita and Associate Professor A. Kida, Department of Otolaryngology, and Professor T. Arikuni, Department of Neuroanatomy, Nihon University School of Medicine, for their encouragement during this research, and Dr A. Okada, Department of Ergonomics, Faculty of Engineering, Chiba University, for the computer programming.

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Ann Otol Rhinol Laryngol 99:1990

DIMENSIONS OF THE SCALA TYMPANI IN THE HUMAN AND CAT WITH REFERENCE TO COCHLEAR IMPLANTS

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The width, height, and cross-sectional area of the scala tympani in both the human and cat were measured to provide dimensional information relevant to the design of scala tympani electrode arrays. Both the height and width of the human scala tympani decrease rapidly within the first 1.5 mm from the round window. Thereafter, they exhibit a gradual reduction in their dimension with increasing distance from the round window. The cross-sectional area of the human scala tympani reflects the changes observed in both the height and width. In contrast, the cat scala tympani exhibits a rapid decrease in its dimensions over the first 6 to 8 mm from the round window. However, beyond this point the cat scala tympani also exhibits a more gradual decrease in its dimensions. Finally, the width of the scala tympani, in both human and cat, is consistently greater than the height.

KEY WORDS — cochlear anatomy, cochlear implant, electrode array, scala tympani.

INTRODUCTION

Knowledge of the dimensions of the scala tympani in both humans and experimental animals is necessary for the continued development of cochlear implants. For example, such information would ensure that scala tympani electrode arrays are not inserted past a point in the cochlea dimensionally smaller than the electrode array. This knowledge would also provide the necessary anatomic information required for the development of improved scala tympani electrode arrays. In addition, comparative data from experimental animals would provide a means of examining the suitability and limitations of animal models that are used in physiologic experiments studying basic neural response properties associated with cochlear implants.

Dimensions of the cochlea in humans and laboratory animals have been reported by several authors.[1-7] However, these reports have some limitations: either the measurements were not made systematically along the scala tympani, or the cross-sectional area, the height, and the width of the scala tympani were not recorded in each cochlea. We required more systematic and detailed measurements of the scala tympani in order to develop improved electrode array designs. Evidence from electrode insertion studies in human temporal bones[8-11] has suggested that the Cochlear Corporation's (Nucleus) banded electrode array lies along the outer wall of the scala tympani. A subsequent histopathologic study of a cochlea from a patient implanted with the banded electrode array confirmed this finding.[12] Moreover, it highlighted the relatively large distance between the electrode array and the residual neural elements within Rosenthal's canal. Recent acute electrical stimulation studies in cats have shown that electrically evoked auditory brain stem response thresholds are reduced and the dynamic range is increased as the banded electrode array is moved from the outer wall of the scala tympani toward the modiolus.[13] These results suggest that an electrode array placed close to the modiolus would be capable of exciting a greater number of discrete groups of auditory nerve fibers, using electrodes with a narrower interelectrode spacing. The development of a more effective electrode array may be possible if the dimensions of the scala tympani are more precisely known.

The present study describes the comparative dimensions of the scala tympani in the human and cat. Silastic molds of the human and cat scala tympani were made, and the width, height, and cross-sectional area were measured every 0.5 mm from the round window.

MATERIALS AND METHODS

Eight human and 10 cat cochleas were used in this study. Cat cochleas were obtained from animals with weights that ranged from 0.35 to 4.0 kg. Human cochleas were obtained from adults. These cochleas were either freshly prepared or stored in a

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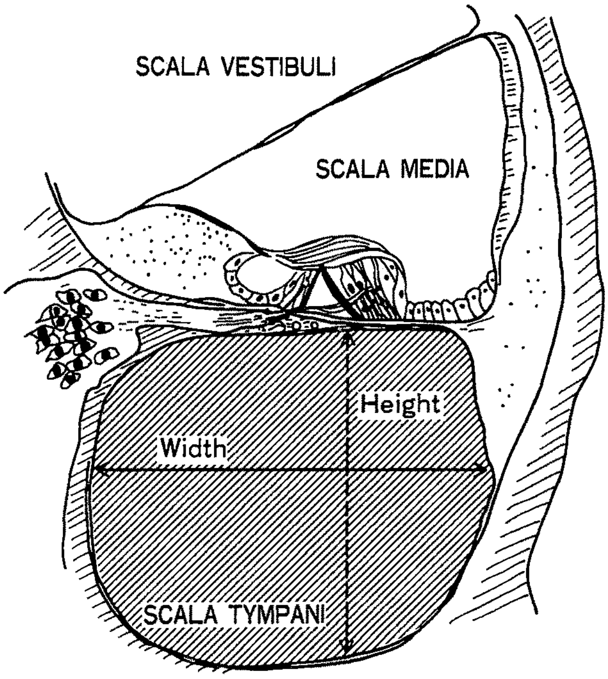

Fig 1. Diagram of scala tympani illustrating three measurements recorded in present study: height, width, and cross-sectional area (shaded) of scala tympani.

deep freezer until required.

Following the resection of the temporal bone, the round window membrane was incised under magnification with use of a hook. Care was taken to avoid damage to the osseous spiral lamina superomedial to the round window. A small hole was made in the apex of the cochlea with a diamond paste drill, the stapes footplate was removed, and the oval window was opened. Each cochlea was then dehydrated in absolute alcohol. To accelerate the dehydration process, each human cochlea was placed under vacuum (−100 kPa) for 15 minutes and then placed in an oven at 70°C overnight.

The Silastic (J RTV silicone rubber) was injected into the scala tympani through the round window. The cochlea was placed under vacuum to assist the infiltration of the Silastic. Finally, the Silastic was allowed to harden at room temperature for 24 hours. The rubber mold of the scala tympani was removed from the cochlea by drilling the overlying bone with use of diamond paste drills under magnification. The rubber mold was then cut at right angles to the basilar membrane. Each section was 0.5 mm thick.

In a preliminary experiment, we had shown that this Silastic was not subject to shrinkage during curing. A resin cast was made, and a mixture of Silastic J RTV was cured in it. The Silastic mold was then removed, and both the cast and the mold were sectioned. Their cross-sectional dimensions were determined by use of a light microscope equipped with a calibrated eyepiece graticule. The outside diameter of the Silastic mold was the same size as the inside diameter of the resin cast, indicating that no shrinkage had occurred.

The cross-sectional area, the width (the widest distance parallel to the basilar membrane), and the height (the longest distance perpendicular to the basilar membrane) of the scala tympani were measured for each 0.5-mm section with use of the graticule and light microscope. The scala tympani measurements we recorded are illustrated in Fig 1. The area, width, and height of the round window were measured from the first 0.5-mm section. This first measurement was made in the plane of the round window. Subsequent measurements from all remaining 0.5-mm-thick sections were made at right angles to the basilar membrane. For each 0.5-mm section, results from the eight human cochleas were combined, and standard deviations were calculated. This procedure was repeated for the data obtained from the 10 cat cochleas.

RESULTS

Shrinkage of the Silastic rubber did not occur. These measurements therefore reflect the absolute dimensions of the scala tympani in both humans and cats.

Although there were difficulties in obtaining accurate molds of the scala tympani in the most apical region of the cochlea, due to the failure of the Silastic to flow into this region, accurate molds of the basal and middle turns were routinely obtained. For this reason, our results are restricted to the basalmost 25 mm of the human cochlea and the basalmost 15 mm of the cat cochlea. These regions, however, cover the maximum insertion distance of a scala tympani electrode array in both human and cat, and are therefore adequate for this study.

The cross-sectional area of the human scala tympani as a function of distance from the round window is illustrated in Fig 2A. For comparison, the cross-sectional area of the Cochlear Corporation's banded scala tympani electrode array is also illustrated in the diagram. As evident from Fig 2A, the cross-sectional area of the human scala tympani exhibits an initial rapid decrease resulting in the halving of the cross-sectional area within the first 1.5 mm from the round window. From this point, the cross-sectional area, which is approximately 2.25 mm^2, gradually reduces with distance from the round window. Twenty-five millimeters from the round window the cross-sectional area of the human scala tympani is approximately 0.75 mm^2.

Figure 2A also illustrates the free-fitting nature of the banded scala tympani electrode array. At the 25-mm point, for example, the electrode array occupies less than 25% of the cross-sectional area of the scala tympani.

The height and width of the human scala tym-

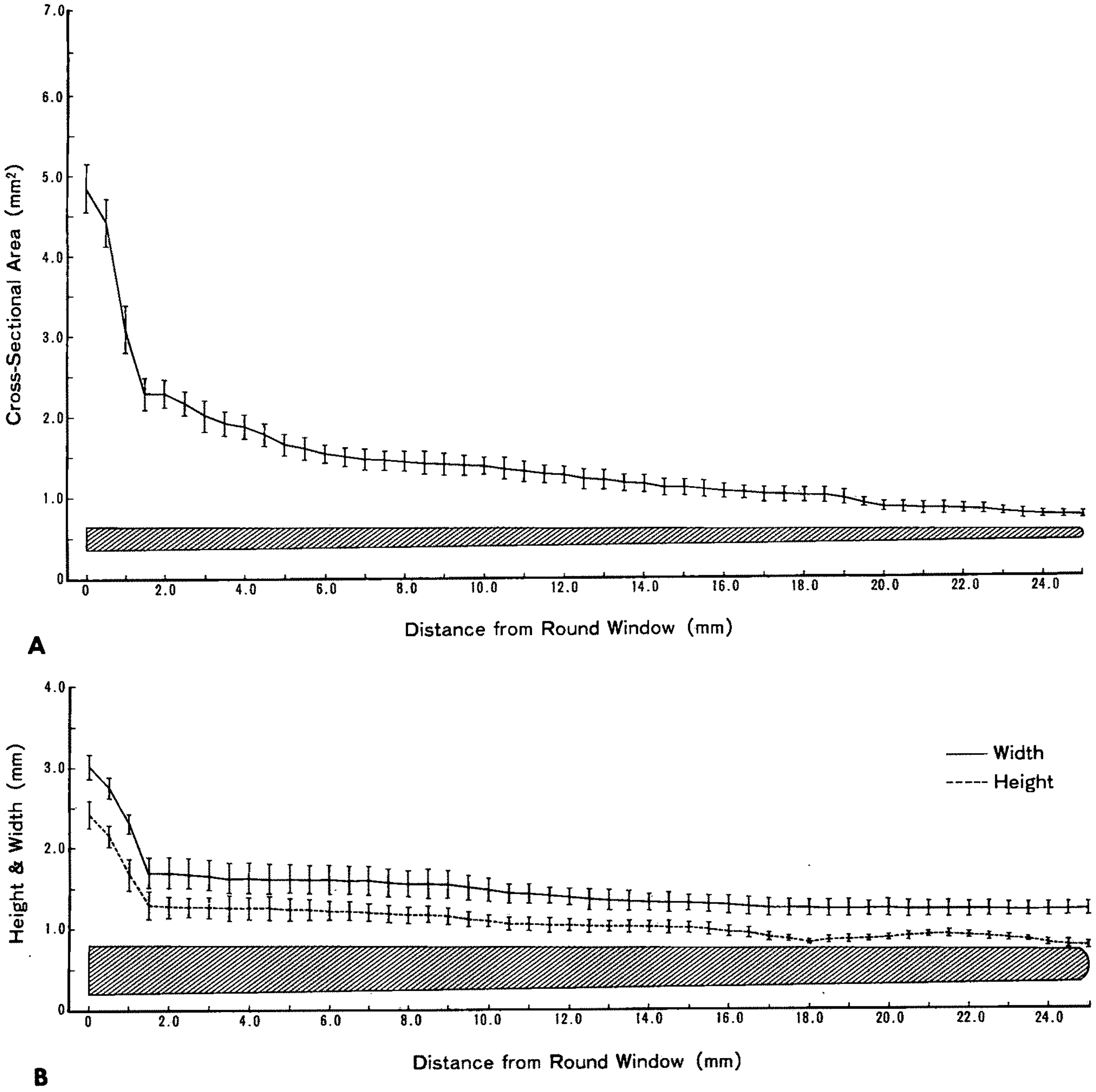

Fig 2. Results of measurements of scala tympani in humans (n = 8). Vertical bars indicate 1 SD, and midpoints indicate mean values. Diagrams of banded scala tympani electrode array (shaded) have been included for comparison. A) Cross-sectional area. B) Width and height. At 25 mm from round window, array represents approximately 50% of height of scala tympani. Height of human scala tympani does not decrease continuously, but shows slight increase in region 18 to 21 mm from round window.

pani, as a function of distance from the round window, are illustrated in Fig 2B and reflect the changes observed in the cross-sectional area. The width of the scala tympani was consistently greater than the height. Although, in general, both the width and height showed a gradual reduction with increasing distance from the round window, the height of the scala tympani did exhibit a sharper reduction, followed by a slight increase in its dimension over a 4-mm region centered around a point 21 mm from the round window.

For comparison, the dimensions of the banded scala tympani electrode array are included in Fig 2B. While the dimensions of the electrode array are somewhat less than the height and width of the scala tympani in the region 25 mm from the round window, the tip of the array is approximately 60% of the height of the scala tympani at this location. This observation should be a consideration if improvements in the design of the electrode array include changes in its dimensions.

The cross-sectional area of the cat scala tympani as a function of distance from the round window is illustrated in Fig 3A. The cross-sectional area of a

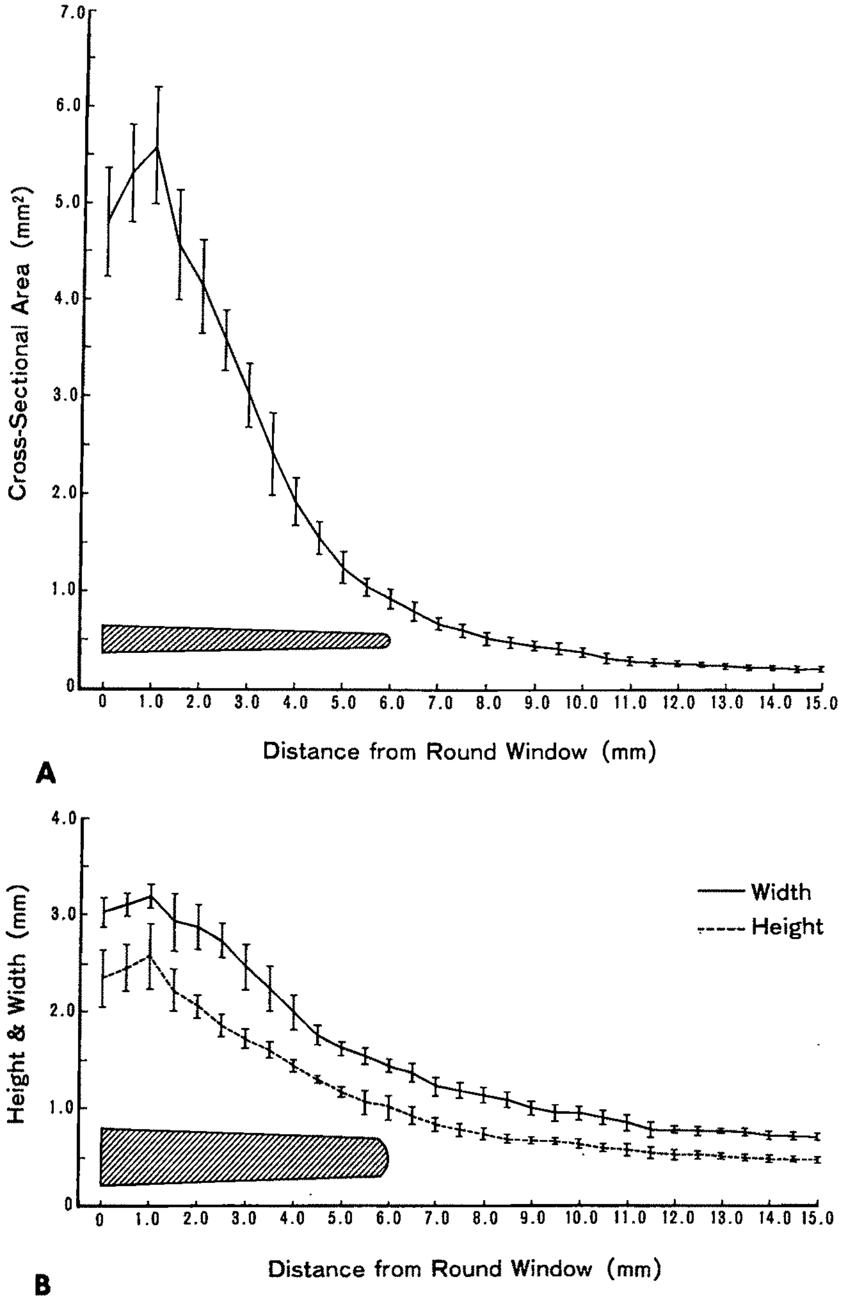

Fig 3. Results of measurements of scala tympani in cats (n = 10). Diagrams of banded scala tympani electrode array (shaded) have been included for comparison. A) Cross-sectional area. B) Width and height. Difference between width and height decreases gradually with increasing distance from round window.

banded scala tympani electrode array — inserted to a distance of 6 mm — is included for comparison. At the round window, the cat scala tympani is almost identical in cross-sectional area to that of the human. This area actually increases over the first millimeter from the round window, but then rapidly decreases over the following 6 to 8 mm, after which it continues to decrease gradually. While in the middle and apical turns the cross-sectional area of the cat scala tympani is 25% to 30% of the human, the cat has a larger scala tympani cross-sectional area than the human within the first 4 mm from the round window.

The height and width of the cat scala tympani as a function of distance from the round window are illustrated in Fig 3B. The changes in these dimensions with distance along the scala tympani reflect the changes observed in the cross-sectional area of the cat scala tympani. As observed in the human, the width of the cat scala tympani is greater than its height. The scala tympani electrode array is usually inserted to a distance of approximately 6 mm from the round window in the cat. At this point the tip of the electrode would occupy approximately 40% to 50% of the height of the scala tympani.

DISCUSSION

The dimensions of the round window in both human and cat are very similar. The cross-sectional area of the human scala tympani then undergoes a

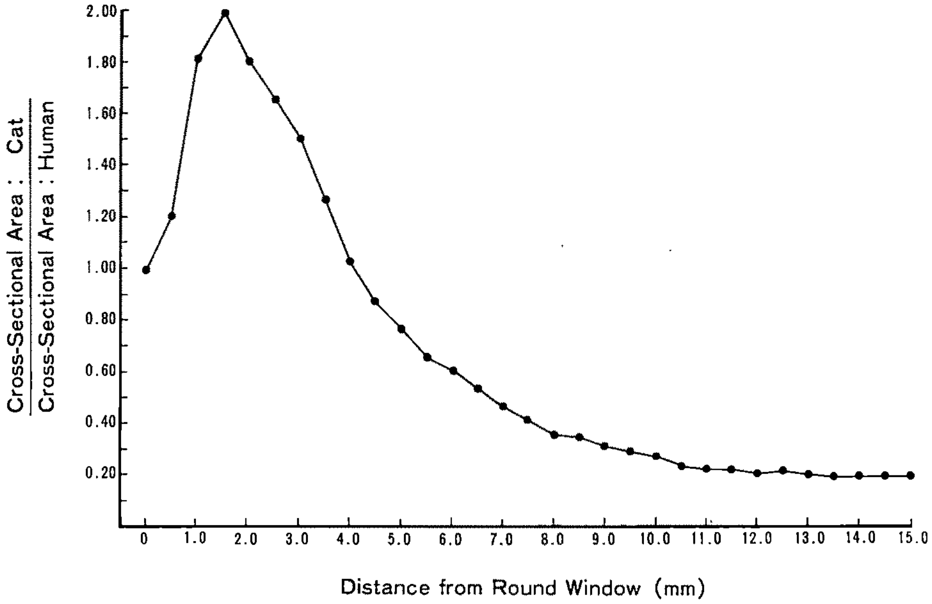

Fig 4. Ratio of cross-sectional area of cat scala tympani to human scala tympani as function of distance from round window.

significant reduction over the next 1.5 mm. This new anatomic finding has not been reported in previous studies, as this region of the scala tympani was not examined in any detail.[6,7] In contrast, the cross-sectional area of the cat scala tympani actually increases over the first 1.0 mm from the round window, and is in fact larger than the human scala tympani in this region. However, the cat scala tympani then funnels dramatically, while the human scala tympani undergoes a very gradual reduction in cross-sectional area with increasing distance from the round window. The ratio of cross-sectional area of the cat scala tympani to that of the human is illustrated in Fig 4.

Our measurements of the width and height of the human scala tympani are in general agreement with the results of Zrunek et al,[7] who recorded the width and height of the human scala tympani at eight specific locations above the round window using resin molds. In addition, our measurements of the cross-sectional area of the scala tympani are similar to the results recorded in the basal and middle turns of the human and cat by Igarashi et al.[6]

In the present study, the height of the scala tympani in the human did not decrease continuously, but showed a slight increase in the region 18 to 21 mm from the round window. A similar observation was made by Zrunek et al.[7] However, they also reported a corresponding increase in the width of the scala tympani in this region. The reason for the discrepancy between the study of Zrunek et al[7] and the present study is not clear. Except for an initial increase in the height and width in the lower basal turn, the cat scala tympani decreased continuously with increasing distance from the round window.

The Cochlear Corporation's banded scala tympani electrode array has a maximum diameter of 0.6 mm and tapers to a tip diameter of 0.4 mm. This electrode array has been designed for insertion to a depth of 25 mm from the round window. At this point, the electrode array is considerably smaller than the scala tympani, occupying less than 25% of its cross-sectional area. However, since the scala tympani is somewhat smaller in height than in width, the electrode array at this point represents at least 50% of the height of the scala tympani, and in some cases significantly more, depending on individual anatomic variations. Therefore, in order to ensure that the dimensions of the electrode array are significantly less than the dimensions of the scala tympani, any future changes in the design of this array should ensure that the tip diameter is not increased.

Our understanding of the physiologic mechanisms associated with electrical stimulation of the auditory nerve via cochlear implants has chiefly come from studies using cats, in which the electrode array is inserted to a depth of 5 to 6 mm from the round window and either evoked potentials or single unit activity is recorded in response to an electrical stimulus. The comparative data in the present study show a significant difference in the relationship of the scala tympani to the electrode array in the human compared with the cat. The rapid decrease in the size of the cat scala tympani adjacent to the 6-mm-long electrode array contrasts with the gradually varying relationship between the electrode array and the dimensions of the human scala tympani beyond the first 1.5 mm. Such a rapid change in the dimensions of the cat scala tympani could result in significant differences in the distance between an electrode and its closest neural elements for several electrodes positioned along the array. This limitation must be taken into account when interpreting physiologic data from this animal model. It may also be worth examining the possibility of using alternative animal models that would allow greater electrode insertion depth while providing less radical changes in the dimensions of the scala tympani.

Future improvements in the performance of patients using cochlear implants may depend on improving both the depth of the electrode insertion and the location of the electrode array within the scala tympani. To do this we need to improve the scala tympani electrode array design while ensuring minimal insertion trauma. The present data provide an anatomic basis for the development of improved scala tympani electrode arrays.

ACKNOWLEDGMENTS — We thank J. E. McNaughtan and D. J. Cook of the Department of Otolaryngology, University of Melbourne, for technical assistance, Dr B. K.-H. G. Franz for providing human material, and J. F. Patrick for critically reading an earlier draft of this paper.

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Ann Otol Rhinol Laryngol 99:1990

MORPHOMETRY OF AMPULLAR DARK CELLS

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The morphologic characteristics of rat ampullar dark cells were analyzed quantitatively. Four parameters were measured: cell area per micron baseline length, membrane surface density, volume density of intercellular space, and volume density of vacuoles. No statistically significant difference was observed for any parameter, either between dark cell regions of the superior, lateral, and posterior ampullae or between different regions of dark cells within a given ampulla. The membrane surface density of the ampullar dark cells was similar to that reported for principal cells of the cortical collecting duct in the kidney. The volume density of the intercellular spaces of the dark cells was very constant, unlike that reported for epithelia involved in isotonic fluid transport. Vacuoles were found to comprise only a small portion of protoplasm in the dark cells. This new morphometry provides a basis on which to examine the response of ampullar dark cells to differing experimental conditions.

KEY WORDS — ampulla, dark cells, morphometry, rat.

INTRODUCTION

Regulation of inner ear fluids has long been a topic of research that today is still unsolved. Fluid microhomeostasis of the endolymph is believed to involve different epithelia, including the stria vascularis of the cochlear duct and dark cell regions of the vestibular end-organs.[1-6] As opposed to the stria vascularis, which is a metabolically more active stratified epithelium and has been the focus of the majority of research in this area, the vestibular dark cells compose a less metabolically active simple epithelium and have been less studied.[7]

The distribution and ultrastructure of vestibular dark cells have been well described in different species.[5,8-12] A role of vestibular dark cells in local homeostasis of endolymph has been conjectured because of several cellular characteristics. Ampullar dark cells contain many basolateral infoldings of their cell membrane, similar to epithelial cells of other ion- or fluid-transporting or -regulating tissues such as the kidney tubule, the choroid plexus, and the ciliary body.[13] The presence of Na-K-ATPase on these basolateral membranes has been demonstrated cytochemically, autoradiographically, and, recently, immunocytochemically.[14-18] Finally, physiologic experiments have shown that these dark cells can absorb methylene blue and ^{22}Na from endolymph.[3,4]

Despite the accumulated data on the cellular features of the vestibular dark cells, quantitative information with regard to their morphologic characteristics has not been reported. A morphometric method has been created to determine volume densities of cells and capillaries of the stria vascularis.[19,20] The objective of this research was to develop an appropriate morphometric method to determine quantitative parameters of normal rat ampullar dark cells upon which to examine the effect of different experimental conditions in the future.

MATERIALS AND METHODS

Tissue Processing. Twelve pigmented Long Evans rats (male, 150 to 250 g) were used in this study. The animals were anesthetized with intramuscular injections of Ketaset (88.0 mg/kg body weight, Bristol Laboratories) and Rompun (13.0 mg/kg body weight, Mobey Corp). Rats were infused via cardiac puncture with 25 mL of phosphate buffer (20 mmol/L sodium phosphate monobasic and 42 mmol/L sodium phosphate dibasic), pH 7.4, followed by 36 mL of fixative (2.5% glutaraldehyde, 0.5% paraformaldehyde in phosphate buffer). Temporal bones were removed following decapitation, and each bulla was opened. The bony labyrinth overlaying the posterior wall of the utricle and superior and lateral ampullae was removed, and fresh fixative was gently perfused onto the vestibular end-organs. Each specimen was submerged in fresh fixative for 1 additional hour, rinsed three times in phosphate buffer, and postfixed for 1 hour in phosphate-buffered 1% osmium tetroxide, pH 7.4. Temporal bones were rinsed three times in phosphate buffer and dehydrated in graded concentrations of ethanol up to a concentration of 70%. Ampullar tissues of the superior, lateral, and posterior semicircular canals were carefully dissected and removed with the aid of a binocular dissecting microscope. The individual ampullar tissues were completely dehydrated and embedded in Epon-araldite

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From the Departments of Anatomy and Cell Biology (all authors) and Surgery (Division of Otolaryngology) (Rarey), College of Medicine, University of Florida, Gainesville, Florida. Funded by the Deafness Research Foundation. This study was performed in accordance with the PHS Policy on Humane Care and Use of Laboratory Animals, the NIH *Guide for the Care and Use of Laboratory Animals*, and the Animal Welfare Act (7 U.S.C. et seq.); the animal use protocol was approved by the Institutional Animal Care and Use Committee (IACUC) of the University of Florida, Gainesville, Florida.

REPRINTS — Kyle E. Rarey, PhD, Box J-235, Dept of Anatomy and Cell Biology, J. Hillis Miller Health Science Center, University of Florida, Gainesville, FL 32610.

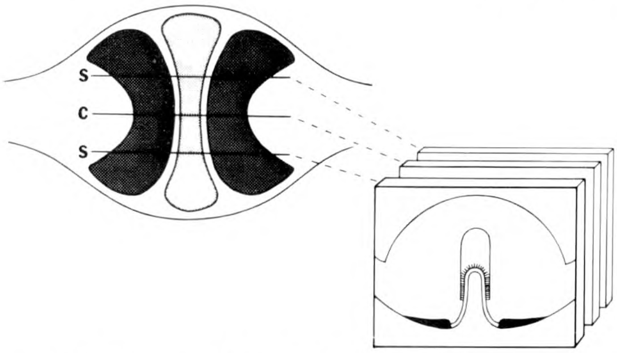

Fig 1. Diagram of dark cell distribution within ampulla. Section of each ampulla was made near center of crista ampullaris (region C), or on either side of center near planum semilunatum (region S). Light-shaded region — crista ampullaris, dark-shaded region — distribution of dark cells.

epoxy resin by routine procedures. All tissues were maintained at 4°C during processing.

Thick (0.9-μm) and ultrathin (70-nm) sections of given ampullar dark cell regions were cut on a Reichert-Jung ultramicrotome with a Diatome MT401 diamond knife. A similar plane of orientation for each ampulla was maintained by sectioning along the apical-basal axis of dark cells at a 90° angle to the length axis of the crista ampullaris. Each section was judged as being cut either through a region in the center (C) of the crista ampullaris or through a region approximate to the planum semilunatum (S) of the crista ampullaris (Fig 1). A section from one dark cell region, either C or S, of the superior, lateral, or posterior ampulla from each of the 12 animals was obtained. Every possible combination of region and ampulla occurred twice. Thick sections were stained with methylene blue and examined under oil immersion. Thin sections were stained with uranyl acetate and lead citrate. Representative samples of dark cells were photographed in a JEOL 100S electron microscope at a magnification of 6,700x. Dark cells nearest to the squamous epithelium were not used because of their transitional morphologic characteristics. Electron micrographs of dark cells at final magnifications of 17,500x were obtained.

Thick-Section Morphometry. Ampullar dark cell regions were morphometrically analyzed with an image analysis system (Southern Micro Instruments) interfaced to an IBM PC/AT microprocessor with a digitizing tablet and high-resolution monitor. Cognizant that individual cell size varies, we performed two quantitative measurements: 1) the area of a given dark cell region and 2) the baseline length of a given dark cell region. By dividing the area by the baseline length, a value representing the size of a given dark cell region was obtained.

Thin-Section Morphometry. Three morphometric parameters of a dark cell region were determined: volume density of intercellular space, volume density of vacuoles, and surface density of dark cell membrane. The volume density of intercellular space and the volume density of vacuoles were determined by use of a point count grid with a systematic lattice (gridline distance: $d = 1.27$ cm; Fig 2). This particular point count grid was chosen such that d^2 was greater than the area of the largest profile encountered.[21,22] The upper right-hand corner of each point was considered to be the true grid intersection. Volume densities were estimated as the sum of point counts overlaying the intercellular space or vacuoles divided by the number of point counts in the reference volume. The reference volume (also referred to as containing volume) for intercellular space measurements was chosen as the total volume of dark cells including intercellular space. The reference volume used when determining volume density of vacuoles was protoplasm.

The surface density of dark cell membrane (Sd),

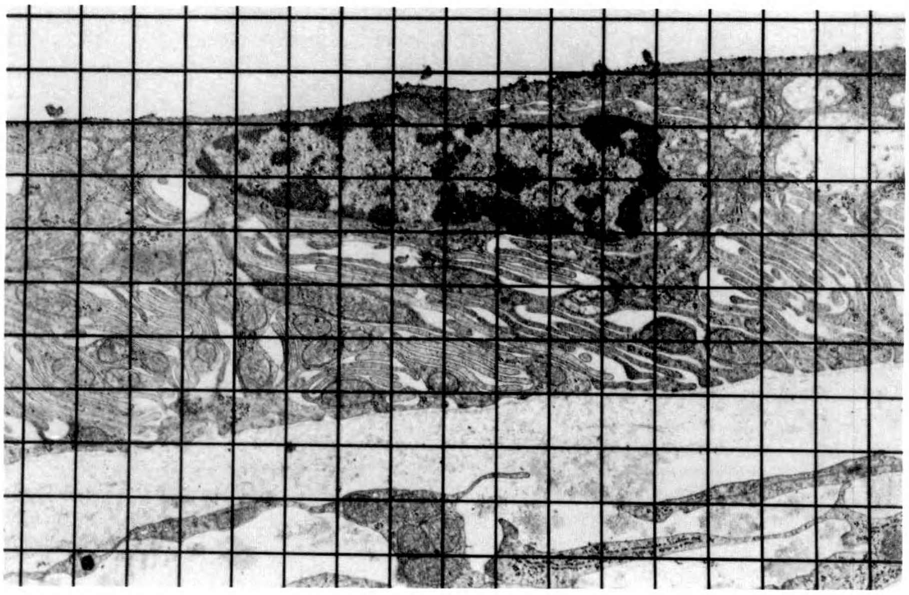

Fig 2. Point count grid overlay placed onto representative photomicrograph of ampullar dark cell region (original x11,000).

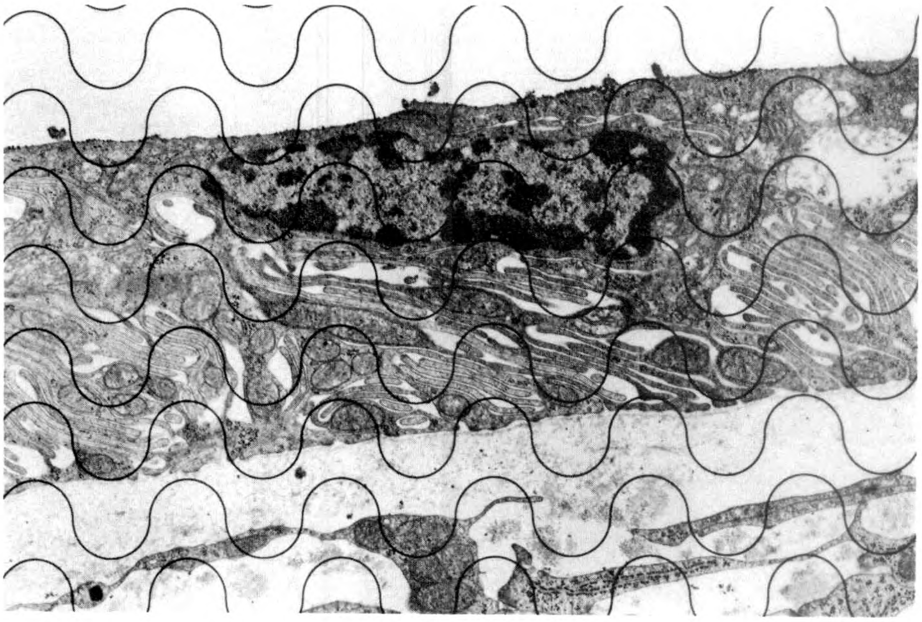

Fig 3. Merz grid overlay placed onto representative photomicrograph of ampullar dark cell region (original x11,000).

defined as surface area of membrane per unit protoplasm, was determined with a Merz grid (gridline distance: $d_m = 1.75$ cm; Fig 3).[23] This grid, developed to compensate for anisotropy of the structure on the micrograph, consisted of horizontal sinusoidal isotropic lines. A correction factor for section thickness was not used, because no absolute data were obtained, even though the diameter of the dark cell infoldings was very small. Moreover, since the orientation distribution of these cellular infoldings was unknown, a correction factor would have been difficult to accurately determine.[21] In order to ensure a surface density relative standard error (RSE) less than 5%, the required gridline length was 56 cm per micrograph (L_t), estimated with the equation $L_t = 4/[S_d \bullet RSE^2]$ (S_d was determined to be on the order of 4.5 $\mu m^2/\mu m^3$, and an average of six micrographs per ampulla were used).[21] With use of a $d_m = 1.75$ cm, approximately 100 cm of gridline length per micrograph was obtained.

The Merz grid was placed on each micrograph and the upper limit of the gridline was followed. Each intersection with dark cell membrane was counted as one, and all apical and basolateral membrane was counted. Surface density was determined[21-23] as $S_d = 2 \bullet I_d$, where I_d is intersection density and was estimated as $I_d = I/[I_m \bullet p]$; I = total number of intersections; I_m = length of gridline between two points; p = point counts in reference volume. Data from individual micrographs were combined and mean values for a given dark cell region were obtained.

Statistical Analyses. Two factors considered to influence the morphometric measurements of a dark cell region were 1) different ampullae (superior, lateral, or posterior) and 2) different ampullar regions (C or S). A two-way ANOVA was employed to compare measurements from different ampullae and from different ampullar regions. The two-way ANOVA also tested for a possible interaction between region and ampullae (ie, a combined effect of region and ampullae on the measurements).

MORPHOMETRY

The morphometry of tissue can be complicated by certain cellular characteristics. For example, ampullar dark cells are polarized. The apical part of a dark cell consists of cytoplasm with vacuoles and other organelles, while the lower half to two-thirds portion of a cell consists mainly of basolateral infoldings (Fig 4). These infoldings are anisotropic, ie, oriented in a preferential direction. Moreover, the density of vacuoles in a given dark cell may vary from apex to base. A method could theoretically be invariant with respect to rotations or translations if a very large number of isotropic sections are analyzed. For practical reasons, in layered structures, the use of sections perpendicular to the layers is preferable, but the angle of cutting does influence the estimations when one is measuring surface density.[21,24] The angle of sectioning is not critical for volumetric analysis even if the structure is anisotropic. Complicated statistical approaches to accurately estimate morphometric parameters of anisotropic structures have been applied to some tissues.[24,25] An alternative method called vertical sectioning can also be used to obtain unbiased surface density estimations for polarized and/or anisotropic structures.[26] Because of the small size and irregular shape of the dark cell regions of the rat ampullae, vertical sectioning could not be utilized. Instead, ampullar tissues were cut in a fixed, similar orientation. Therefore, data obtained using this method are not absolute, but are reproducible and can reliably be used on a comparative basis.

Changes in reference volume lead to discrepan-

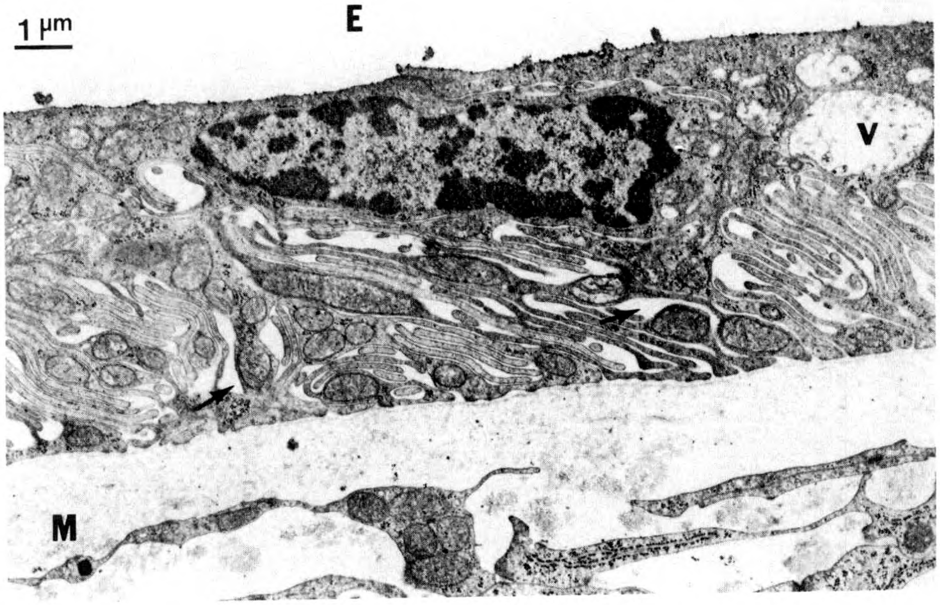

Fig 4. Representative electron micrograph of dark cell. Observe polarity of dark cell. Infoldings of plasmalemma and intercellular spaces (arrows) are basolateral in position, and vacuoles (v) and nucleus are located more apically. Melanocyte (M) is seen in subepithelial zone. E — endolymph.

cies in surface density and volume density, since these are denoted as per unit volume. By measuring cell area per baseline length, variations in reference volume can be suspected. It is also possible to estimate data per micron baseline length to avoid influence of reference volume changes.[21]

RESULTS

Means and standard errors of the cell area per micron baseline length, of the membrane surface density, of the volume density of intercellular space, and of the volume density of vacuoles for the ampullar dark cell regions of the superior, lateral, and posterior ampullae are presented in the Table. Means and standard errors of the parameters obtained for region C or region S of a given ampulla are also presented in the Table. No statistically significant differences (two-way ANOVA, $p < .05$) either between the dark cell regions of superior, lateral, and posterior ampullae or between regions C and S were found for each measured morphologic feature. The statistical test showed no significant interaction between region and ampullae.

DISCUSSION

No statistically significant differences in cell area per micron baseline length, membrane surface density, volume density of intercellular space, and volume density of vacuoles were observed between dark cell regions of the superior, lateral, and posterior ampulla. These data support the impression in the literature that dark cell regions of different ampullae are similar.[8]

Findings of this study also demonstrated that dark cell regions in different locations of an ampulla did not differ with respect to the morphologic characteristics measured. Until now there have been no data regarding similarities of different ampullar dark cell regions. Dark cell regions (C and S) from the same ampulla were compared in an earlier pilot study, and similar data were obtained for each region. These findings collectively imply that random regions of different ampullae can be used when comparing experimental groups, unless there is reason to assume these would be affected differently.

The membrane surface densities of ampullar dark cells were similar to those measured by an analogous method in the principal cells of the cortical collecting duct.[27,28] The ampullar dark cells and the renal principal cell have similar basolateral membrane configurations, and their apical membranes contain few microvilli. Principal cells are thought

MORPHOMETRIC DATA OF AMPULLAR DARK CELLS

	Superior Ampulla (N = 4)	*Lateral Ampulla (N = 4)*	*Posterior Ampulla (N = 4)*	*Region C (N = 6)*	*Region S (N = 6)*
Cell area per baseline length ($\mu m^2/\mu m$)	8.2 ±0.22	8.1 ±0.79	7.0 ±0.35	7.5 ±0.57	8.0 ±0.31
Membrane surface density ($\mu m^2/\mu m^3$)	9.07 ±0.46	7.89 ±0.42	8.24 ±0.46	8.21 ±0.40	8.49 ±0.42
Intercellular space volume density ($\mu m^3/\mu m^3$)	0.15 ±0.02	0.12 ±0.02	0.13 ±0.01	0.12 ±0.01	0.14 ±0.02
Vacuole volume density ($\mu m^3/\mu m^3$)	0.042±0.011	0.045±0.007	0.046±0.011	0.036±0.003	0.053±0.009

Values are means ±SEM. No statistical differences (two-way ANOVA, $p < .05$) were found between different ampullae or between different regions for each morphologic parameter.

Region C — region in center of crista ampullaris, region S — region approximate to planum semilunatum of crista ampullaris.

to be involved in sodium absorption and potassium secretion,[28] and are situated in a microenvironment comparable to endolymph, since a high potassium concentration can be created and maintained in the lumen of the cortical collecting duct.[29] Such similarities are suggestive of a functional role of dark cells in regulating the Na^+ and K^+ concentrations of endolymph.

Basolateral membrane surface density of frog dark cells has been previously determined by a different morphometric method.[14] The membrane surface density of frog ampullar dark cells was found to be lower than that of the rat, even though the apical part of the frog dark cells was not included in the reference volume.

In contrast with an earlier qualitative observation,[16] the volume density of intercellular space in the different ampullar dark cell regions was uniform. Ampullar dark cells appear to differ in this respect from epithelia that are involved in isotonic fluid transport, like that of the gallbladder, intestine, and proximal nephron.[30,31] Large variations in intercellular space have been observed and correlated with different physiologic states in these epithelia.

Vacuoles of various sizes were a minor content of the ampullar dark cell protoplasm. The origin and precise function of the vacuoles is unknown, but experiments suggest they may be involved in absorption. For example, after endolymphatic injection, methylene blue was found to accumulate in vacuoles of dark cells.[3,4] Further, an increase in the number of vacuoles was observed after the addition of up to 5% NaCl to the endolymph,[4] yet vacuoles increased in other cells that were bathed with a hypertonic solution and were found not to be a major shunt pathway.[32]

The morphometric method applied in this study has proven practical in obtaining nonarbitrary quantitative data. Much remains to be known about the ampullar dark cells. As in renal research, application of morphometric methods under various experimental conditions can contribute to the further understanding of the function of ampullar dark cells.

ACKNOWLEDGMENT — The authors thank Dr Kirsten M. Madsen for her helpful comments in the preparation of this manuscript.

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INTERNATIONAL HEARING AID CONFERENCE: SIGNAL PROCESSING, FITTING, & EFFICACY

The International Hearing Aid Conference: Signal Processing, Fitting, & Efficacy will be held June 21-23, 1991, at The University of Iowa, Iowa City, Iowa. The organizing committee includes Richard S. Tyler, PhD (Signal Processing), Chaslav V. Pavlovic, PhD (Fitting), and Ruth A. Bentler, PhD (Efficacy). Further information may be obtained from any member of the organizing committee at the Department of Speech Pathology and Audiology, The University of Iowa, Iowa City, IA 52242; (319) 335-8726, FAX (319) 335-8851.

Ann Otol Rhinol Laryngol 99:1990

HEAD STABILITY AND GAZE DURING VERTICAL WHOLE-BODY OSCILLATIONS

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To understand head and eye stabilities during upright locomotion, we investigated head and eye movements during vertical whole-body oscillations of various amplitudes (1 to 10 cm) and frequencies (1 to 3 Hz) in both normal subjects (n = 10) and patients with bilateral labyrinthine loss (n = 5). Vertical oscillations produced pitching motions of the head, of which the amplitude was markedly altered by a change in the oscillation frequency or the displacement. Vertical eye movements, being correlated with pitching head movements, were scarcely modified by gaze at 2 and 3 Hz. Acquired bilateral lesions presented deteriorated head stability and physically induced eye movements under stronger stimulations. However, significant increase of head movement upon stepping and suppression of pitching motion upon running, both characteristically found in bilateral lesions, were not reproduced by passive oscillations. Thus, these features during active locomotion may result from imbalance produced by alternate bipedal motions and from adaptation to minimize oscillopsia, respectively.

KEY WORDS — head stability, labyrinthine dysfunction, oscillopsia, vertical oscillation.

It is well known that patients with bilateral labyrinthine loss complain of oscillopsia (blurring of the visual surroundings) during upright locomotion as well as daily head movements. Oscillopsia may reflect the perception of retinal image slip induced by dysfunction of the vestibulo-ocular reflex. Several factors to modify deficient compensation and perception have been proposed: development of the cervico-ocular reflex,[1-3] the ability to suppress retinal image slip at a higher perceptive mechanism,[3,4] the otolith function, etc. Our previous studies indicated that whereas the head is strictly stabilized during stepping in normal subjects, patients with bilateral labyrinthine loss presented larger and irregular displacements (right-left, forward-backward) on the horizontal plane.[5] On the other hand, rhythmic pitching head movements, being characteristic of running in normal subjects, were rather suppressed in patients with bilateral lesions.[5] The result suggested that not only deficient compensation but also the nature and magnitude of head movement may participate in the occurrence of oscillopsia during upright locomotion.

In order to know the effect of vertical oscillation on the head and gaze stability during upright locomotion, we investigated head movements and eye movements under vertical whole-body oscillations in both normal subjects and patients with bilateral loss of labyrinthine function.

METHODS

Vertical whole-body oscillations were given by an electrically driven platform that vertically and sinusoidally oscillated a subject standing on the platform at the frequencies of 1, 2, and 3 Hz. The amplitude of vertical displacement was altered from 1 cm to 10 cm. The maximal oscillation amplitude at 3 Hz was at most 5 cm, since the subject hopped on the platform under larger oscillations, making it difficult to obtain accurate recordings. Oscillations of 1 cm at 2 Hz were comparable to stepping (0.8 cm, 2 Hz), and those of 4 cm at 3 Hz to running (5.5 cm, 3 Hz),[5] since actual head displacement amounted to 5.1 cm and 6.6 cm at the oscillation amplitudes of 4 cm and 5 cm, respectively, at 3 Hz. Pitching head movements were recorded by a gyrosensor. To know the magnitude of vertical and forward-backward linear displacement of the head, we took stroboscopic pictures of 10-cm-long fluorescent bars put on the side of the face at the rate of 10 Hz for a second. Vertical eye movements were recorded by a DC electro-oculograph.

The subjects underwent the tests after being in the dark room for 10 minutes. During the tests, they were asked to stand on the platform with the feet arranged, to hold their arms lightly on the platform, and to accept platform oscillations. Oscillation amplitude was increased from 1 cm to 10 cm (1 cm to 5 cm at 3 Hz) by 1-cm increments at 1, 2, and 3 Hz, in which oscillations lasted for at least 10 seconds. To know the effect of gazing at a target on the head and eye stability, head movements and eye movements were recorded under two different visual conditions: with the subject fixating on a small red lamp 150 cm in front of the eyes and with the eyes open in the dark.

We measured the linear displacement (centimeters) and the rotation amplitude (degrees) of the head and the amplitude of vertical eye movement on the most stable recordings, and compared this with the findings obtained under stepping and running that were already reported,[5] both in normal

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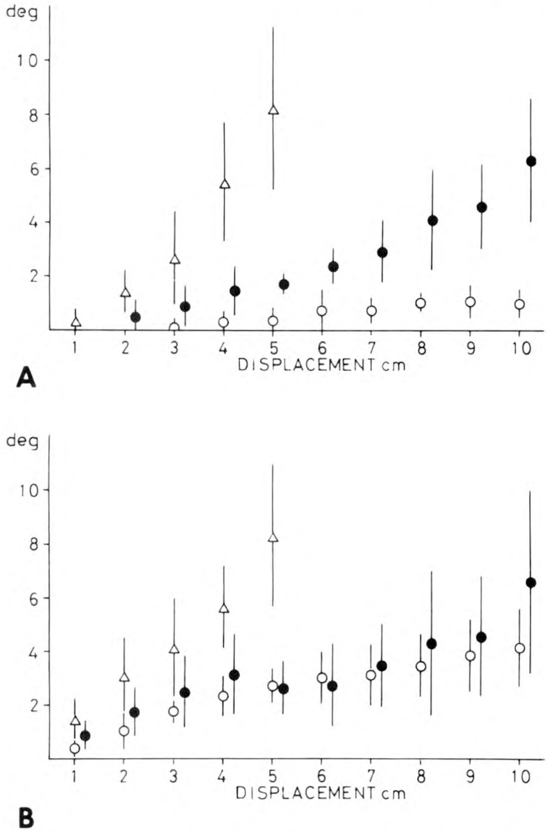

Fig 1. Mean and SD of A) pitching head angle and B) amplitude of vertical eye movement in light in normal subjects (n = 10) under oscillations at 1 Hz (open circles), 2 Hz (filled circles), and 3 Hz (triangles).

subjects and patients with bilateral labyrinthine loss. Since vertical eye movements were minute and distorted by concomitant palpebral movements, we measured the amplitude, but not the slow-phase eye velocity or the vestibulo-ocular response gain. We have ascertained the accuracy of vertical eye amplitude at least within the range of ±10°.

SUBJECTS

The subjects consisted of 10 normal adults (5 men and 5 women; mean age, 26.5 years) and 5 patients with bilateral loss of labyrinthine function who showed no response upon ice water irrigation. Four patients with acquired lesions were 39-, 56-, and 79-year-old men who suffered from streptomycin intoxication 7, 4, and 6 years before, respectively, and a 42-year-old woman who lost labyrinthine function from an unknown cause 20 years before. The three male patients complained of oscillopsia upon walking. The other patient was a 34-year-old man with bilateral congenital inner ear anomalies who had worked as a fisherman and had never complained of oscillopsia.[6] They at the same time underwent passive rotation tests (40° amplitude, 0.2 to 0.85 Hz),[7] and manifested low vestibulo-ocular reflex gain values (0.41, 0.26, 0.34, 0.55, and 0.16 at 0.85 Hz) and marked impairments of spatial gaze stabilization at high frequencies.

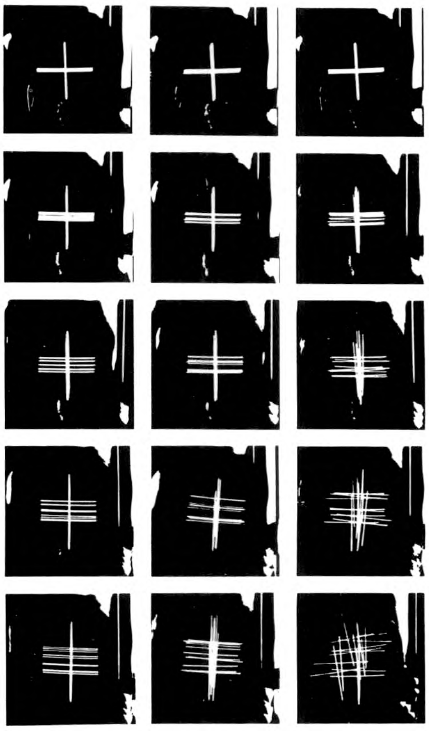

Fig 2. Stroboscopic pictures of fluorescent bars in test of normal subject. From top to bottom, recordings under displacement of 1, 2, 3, 4, and 5 cm, and from left to right, recordings at 1, 2, and 3 Hz, respectively.

RESULTS

Normal Subjects. Whereas pitching motions of the head were scarcely induced during oscillations at 1 Hz (mean, 1.0° ±0.5° at 10 cm displacement), they increased in proportion to an increase in the vertical displacement at 2 Hz (Fig 1). Pitching head movements enlarged steeply at 3 Hz from a mean of 0.3° at 1 cm to 8.2° at 5 cm (Figs 1 and 2). Linear head displacement for a second in the forward-backward direction was a mean of 1.5 cm under oscillations of 10 cm at 1 Hz; it amounted to 3 cm under oscillations of 10 cm at 2 Hz and of 5 cm at 3 Hz (Figs 2 and 3). Head movements did not differ in the light and in the dark.

The amplitude of vertical eye movement in the light exceeded that of pitching head movement under oscillations at 1 Hz and oscillations of small amplitude at 2 Hz and 3 Hz; however, the former became close to the latter under larger displacements (Fig 1 and Table 1). Oscillations in the dark resulted in similar findings, except for smaller eye movements under weak stimulations (Table 1); the mean ratio of eye amplitude to head amplitude was 1.00 to 1.06 under oscillations of 6 to 10 cm at 2 Hz, and 0.98 to 1.26 under those of 3 to 5 cm at 3 Hz.

Compared with the findings under stepping and running, simulative passive oscillations in the light produced smaller forward-backward displacement of the head (mean, 0.3 times) and smaller vertical eye movement (mean, 0.5 times) at 2 Hz, but larger

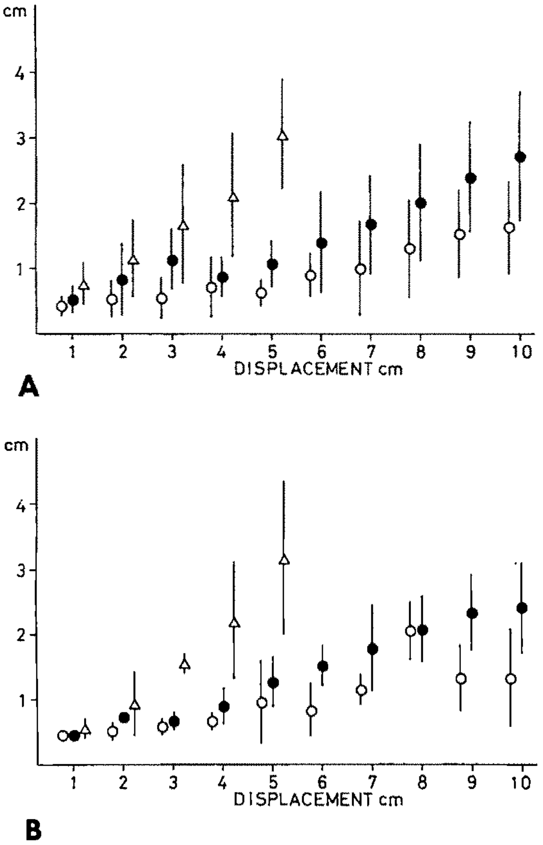

Fig 3. Mean and SD of forward-backward head displacement in light under oscillations at 1 Hz (open circles), 2 Hz (filled circles), and 3 Hz (triangles). A) Normal subjects (n = 10). B) Patients with acquired lesions (n = 4).

pitching motions (mean, 1.3 times) and vertical eye movements (mean, 1.8 times) at 3 Hz (Table 2[5]).

Patients With Bilateral Labyrinthine Loss. Pitching motions of the head in acquired bilateral lesions resembled those found in normal subjects under weak stimulations; however, they became more variable under stronger stimulations, and the mean values exceeded normal ones (Figs 4 and 5). In contrast, the patient with congenital inner ear anomalies presented much smaller pitching motions (Figs 6 and 7). Forward-backward movements resembled normal ones at all the frequencies (Fig 3). Even in bilateral lesions, vision did not affect the magnitude of head movement.

As regards vertical eye movements in acquired lesions, the amplitude in the light resembled the normal one under oscillations with small displacements, but it exceeded the normal value under larger oscillations, in accordance with larger pitching head movements (Fig 4). In the anomaly case, eye movements were significantly smaller than those in acquired lesions, corresponding to smaller head movements (Figs 6 and 7). Whereas the ratio of eye amplitude to head rotation amplitude in the dark was not less than normal in acquired lesions (mean, 0.86 to 1.38 at 2 Hz and 6 to 10 cm; 1.42 to 1.50 at 3 Hz and 3 to 5 cm), the anomaly case showed smaller values (0.67 to 1.12 at 2 Hz and 6 to 10 cm; 0.51 to 0.58 at 3 Hz and 3 to 5 cm). The effect of gaze on vertical eye movement was similar to that in normal subjects (Table 1). Aggravated head stability upon stepping and decrease of pitching head movement upon running, being characteristic in patients with bilateral lesions during upright locomotion,[5] were not observed during passive oscillations.

TABLE 1. DATA COMPARISONS

Displacement (cm)	Subjects	*Head Amplitude Versus Eye Amplitude in Light*			*Head Amplitude Versus Eye Amplitude in Dark*			*Eye Amplitude in Light Versus in Dark*		
		1 Hz	*2 Hz*	*3 Hz*	*1 Hz*	*2 Hz*	*3 Hz*	*1 Hz*	*2 Hz*	*3 Hz*
1	NS	p = .01	p = .01	p = .01	p = .05	p = .01	p = .05			
	AL									
2	NS	p = .01	p = .05	p = .05	p = .05	p = .05				
	AL		p = .01						p = .01	
3	NS	p = .01	p = .05		p = .05			p = .05		
	AL	p = .01	p = .01					p = .05		
4	NS	p = .01	p = .05		p = .05			p = .05		
	AL	p = .01	p = .05					p = .01		
5	NS	p = .01			p = .01	p = .05		p = .05		
	AL	p = .01			p = .05			p = .05		
6	NS	p = .01		—	—			p = .01		—
	AL	p = .01						p = .01		
7	NS	p = .01		—	p = .05		—	p = .05		—
	AL	p = .01						p = .05		
8	NS	p = .01		—	p = .01		—	—		
	AL	p = .05			p = .01					
9	NS	p = .01		—	—			p = .05		—
	AL	p = .01						p = .01		
10	NS	p = .01		—	p = .05		—	p = .05		—
	AL	p = .01			p = .05			p = .05		

NS — normal subjects, AL — subjects with acquired lesions, dashes — not performed, blank spaces — no significant difference.

TABLE 2. VERTICAL AMPLITUDE OF MOVEMENT IN DEGREES (MEAN±SD)

	*Active Locomotion**		*Passive Oscillation*	
	Head	*Eye*	*Head*	*Eye*
2 Hz				
Normal (n = 10)	0.3±0.5	1.7±1.7	0.0	0.9±0.5
Acquired lesions (n = 4)	2.1±0.5	2.9±1.7	0.1±0.2	0.3±0.3
Congenital anomalies (n = 1)	2.8	1.9	0.5	0.3
3 Hz				
Normal (n = 10)	4.3±1.9	3.3±2.1	5.5±2.2	5.6±1.5
Acquired lesions (n = 4)	2.3±0.4	3.8±1.8	5.0±3.0	7.4±4.2
Congenital anomalies (n = 1)	2.3	4.2	3.7	1.6

*Data from Takahashi et al.[5]

DISCUSSION

Patients with bilateral loss of labyrinthine functions consistently complain of oscillopsia. The complaint is most commonly experienced during upright locomotion like walking and running.[8] The patients also perceive blurring of visual surroundings upon fast head rotations.[9,10] However, there are several important differences between voluntary head movements and head movements during upright locomotion; whereas the former are in general active, one-way movements of a middle frequency range, the latter are passively induced, repetitive movements of a high frequency range.[11,12] There have been only a few reports as regards the effect of vertical oscillation upon head and eye stability.[13,14] Therefore, in the present study, we reproduced sinusoidal, vertical oscillations of various frequencies and amplitudes, including those comparable to stepping and running in place,[5,12] and investigated head and eye stabilities and the effect of labyrinthine dysfunction upon them.

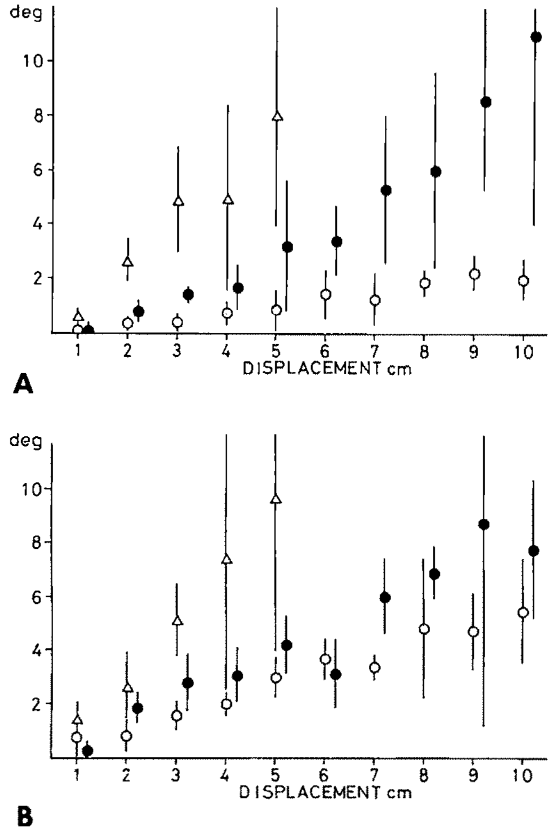

Fig 4. Mean and SD of A) pitching head angle and B) amplitude of vertical eye movement in light in patients with acquired lesions (n = 4) under oscillations at 1 Hz (open circles), 2 Hz (filled circles), and 3 Hz (triangles).

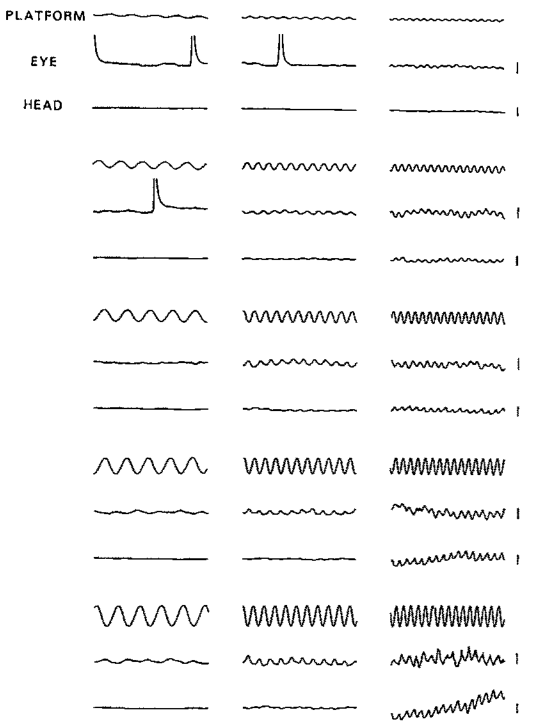

Fig 5. Recordings of eye and head movements in patient with acquired bilateral lesions. From top to bottom, recordings under displacement of 1, 2, 3, 4, and 5 cm, and from left to right, recordings at 1, 2, and 3 Hz, respectively. Vertical bars indicate 10°.

Vertical, sinusoidal oscillations of the whole body rhythmically produced pitching motions of the head accompanying forward-backward linear displacements, of which the amplitude was markedly altered by a change in the magnitude or the frequency of vertical displacement. Since these head movements were scarcely influenced by vision, they should depend on the magnitude of vertical linear acceleration. Although the efficiency of bipedal motions has been investigated by analysis of linear body movements or mechanical power spent,[15-18] secondarily induced pitching motions may play a crucial role in deciding the frequency and amplitude of bipedal motions as well as in securing gaze stabilization. Greater and more variable pitching movements in acquired bilateral lesions may indicate degraded head stability in space against the im-

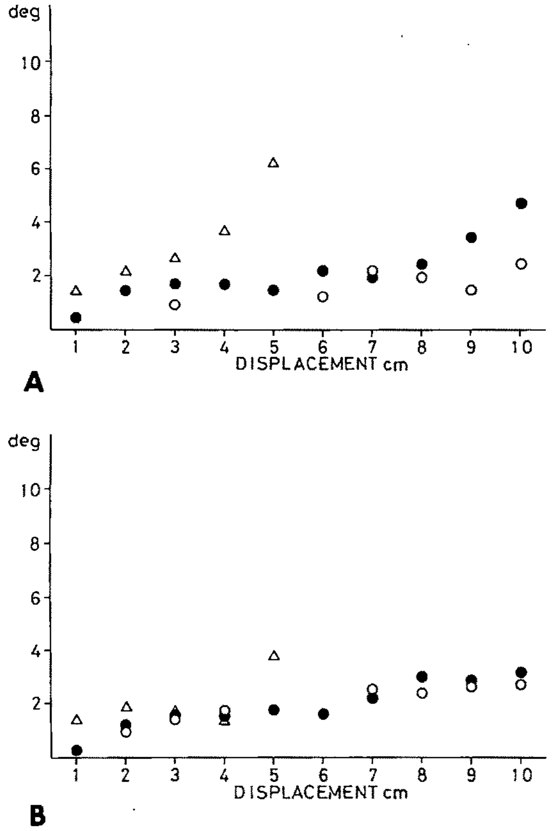

Fig 6. Mean of A) pitching head angle and B) amplitude of vertical eye movement in light in patient with congenital inner ear anomalies under oscillations at 1 Hz (open circles), 2 Hz (filled circles), and 3 Hz (triangles).

pact of vertical acceleration. In contrast, the smaller pitching movement found in the anomaly case seemed to be part of an adaptive process to minimize deficient compensation.

The amplitude of vertical eye movement under oscillations at 2 and 3 Hz depended on that of pitching head movement in both normal subjects and patients, irrespective of gazing at a target. Whereas the mean ratio of eye amplitude to head rotation amplitude in the dark at 3 Hz (3 to 5 cm) resembled unity in normal subjects, it was rather enlarged in acquired bilateral lesions (1.4 to 1.5) and was suppressed in the anomaly case (0.5 to 0.6). The result indicates that in normal subjects, vertical linear accelerations are transformed into rhythmic pitching motions that induce compensatory eye movements, making the gaze horizontal. On the other hand, degraded head stability combined with intensive oscillations produced large pitching motions in acquired lesions, which possibly caused physically induced eye movements. Depression of pitching motion exempted the anomaly case from physically induced eye movements. Thus, we suspect that a decrease in the vertical oscillation upon running in patients with bilateral labyrinthine loss[5] may be profitable in suppressing pitching motions, resulting in better gaze stabilization.

The findings of vertical eye movements differed from those observed during voluntary, high-frequency head oscillations on the horizontal plane, in which normal subjects and patients with bilateral lesions presented significant increase and decrease, respectively, of eye amplitude relative to head movement.[19] Different from a previous report,[13] the present study suggests that provided the otolith possesses the function to stabilize the eyes, its dysfunction rather magnifies vertical eye movements during vertical oscillations. Furthermore, we can say that target presentation was unable to affect gaze stabilization under high-frequency oscillations, irrespective of the state of vestibulo-ocular reflex function. The rule was common to the eye movements under horizontal rotations.[7,19]

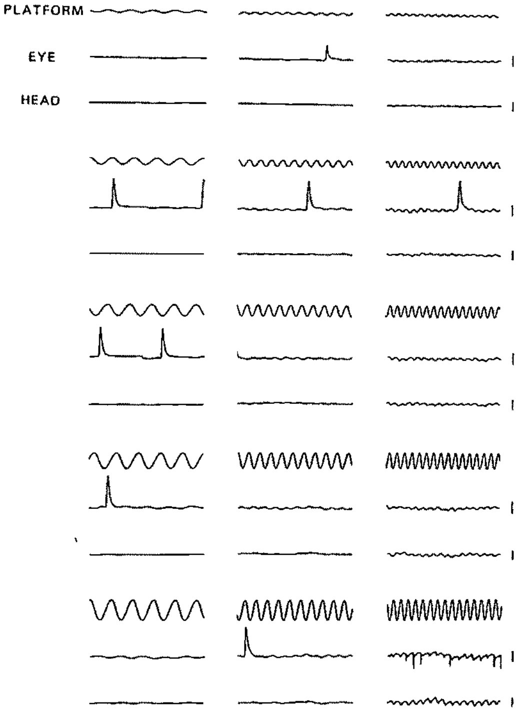

Fig 7. Recordings of eye and head movements in patient with congenital inner ear anomalies. From top to bottom, recordings under displacement of 1, 2, 3, 4, and 5 cm, and from left to right, recordings at 1, 2, and 3 Hz, respectively. Vertical bars indicate 10°.

Passive oscillations (2 Hz, 1 cm) simulating stepping could not reproduce the large pitching motions (mean, 2.1°) or forward-backward head movements (mean, 4.3 cm) found in bilateral lesions.[5] Therefore, degraded head stability upon stepping in bilateral lesions should be related to perturbations resulting from alternate bipedal motions rather than vertical body oscillations themselves. Similarly, since suppression of the pitching head movement[5] did not occur under platform oscillations simulating running in acquired lesions, it may be actively initiated upon running in bilateral lesions to overcome deficient compensation. The difference in the findings between active locomotion and passive oscillations may be partly explained by the hypothesis of top-to-down regulation proposed by

Berthoz and Pozzo[20] that gaze controls posture and head stability during active motions, rather than the balance of the body regulating head and gaze stability. In bilateral lesions — even with the vertical oscillation decreased — magnified, irregular head movements, both linear and rotatory, during upright locomotion should deteriorate deficient compensation and result in marked slippage of the visual surroundings, since vision is unable to affect gaze under high-frequency head movements.

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FIRST INTERNATIONAL CONFERENCE ON ACOUSTIC NEUROMA

The First International Conference on Acoustic Neuroma will be held Aug 25-29, 1991, in Copenhagen, Denmark. For further information, contact Copenhagen Acoustic Neuroma Conference, Secretariate, ENT Department, Gentofte University Hospital, DK-2900 Hellerup, Copenhagen, Denmark.

Ann Otol Rhinol Laryngol 99:1990

MANAGEMENT OF TRACHEOBRONCHIAL FOREIGN BODIES IN CHILDREN: AN UPDATE

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BOSTON, MASSACHUSETTS

Tracheobronchial foreign bodies continue to be a source of morbidity and mortality in the pediatric population. Technical advances in anesthesia and equipment have made the removal of these troublesome objects more feasible. Diligence must still be exercised and a coordinated team effort must be employed in order to achieve a satisfactory and safe outcome for the patient. The appropriate use of diagnostic studies and management techniques are discussed.

KEY WORDS — children, endoscopy, foreign bodies, tracheobronchial tree.

INTRODUCTION

The aspiration of foreign bodies into the aerodigestive tract continues to be an important cause of morbidity and mortality. This problem is responsible for many deaths each year worldwide, with children under 2 years of age being the most commonly affected. Children in this age group frequently place objects into their mouths, thus increasing the chance for aspiration.

Those patients who survive the acute incident may present even the most experienced endoscopist with a challenge in both diagnosis and treatment. Advances in radiology, anesthesia, and endoscopic instrumentation have led to improved patient care and also now point to the need to develop a qualified "team" that includes a radiologist, an anesthesiologist, and an endoscopist.

Unfortunately, patients who suffer complete airway obstruction immediately following an acute aspiration almost never reach the hospital in time to have a favorable outcome. Thus, the Heimlich maneuver has become the single most important mechanism in these extreme situations.[1] In many cases, however, the condition of the patient allows for a more deliberate and thoughtful consideration of the physiologic and mechanical factors involved.

DIAGNOSIS

The diagnosis of acute aspiration is usually straightforward. Initially there may be a specific episode of choking, coughing, gagging, or wheezing. On occasion there may be associated hoarseness, aphonia, or dysphonia. Objects impacted in the trachea may also cause audible stridor, usually biphasic or expiratory.

An accurate history is extremely useful in making the diagnosis, and thus parents should be questioned carefully regarding the possibility of foreign body aspiration in any patient with respiratory symptoms or swallowing disorders. It is not uncommon for historical facts given by parents and/or the patient to be overlooked or underappreciated. In these cases patients may be treated for long periods of time for other disorders such as asthma or recurrent pneumonia, as many aspirations occur in the same age group that has a high incidence of these disorders. Unexplained recurrent pneumonia, "atypical asthma," or recurrent respiratory illness that does not respond to adequate medical therapy should always raise the suspicion of an aspirated foreign body.[2]

Careful auscultation of the chest is extremely useful in finding subtle differences between the right and left sides. Such differences should always raise one's suspicion. In addition, unilateral wheezing is very suggestive of foreign body impaction.

RADIOGRAPHIC EVALUATION

Plain radiographs of the neck and chest are basic in the evaluation of any patient suspected of having aspirated a foreign object, but in and of themselves do not constitute a complete examination. In some cases the findings of these studies may even be normal.

The cross-sectional area of the airway increases during inspiration, and thus foreign bodies tend to move peripherally during this phase of respiration. If the object is positioned to allow airflow during inspiration with occlusion during expiration, it will act as a check valve. The result is hyperinflation of the lung distal to the object in question, and depression of the ipsilateral hemidiaphragm with a shift of mediastinal structures to the opposite side (see Figure, A).

If the object completely obstructs the airway as it progresses distally, complete endobronchial obstruction ensues, with resulting atelectasis (see Figure, B). Fluoroscopy may be helpful in detecting the presence of a foreign body in the airway. Mediastinal shift and

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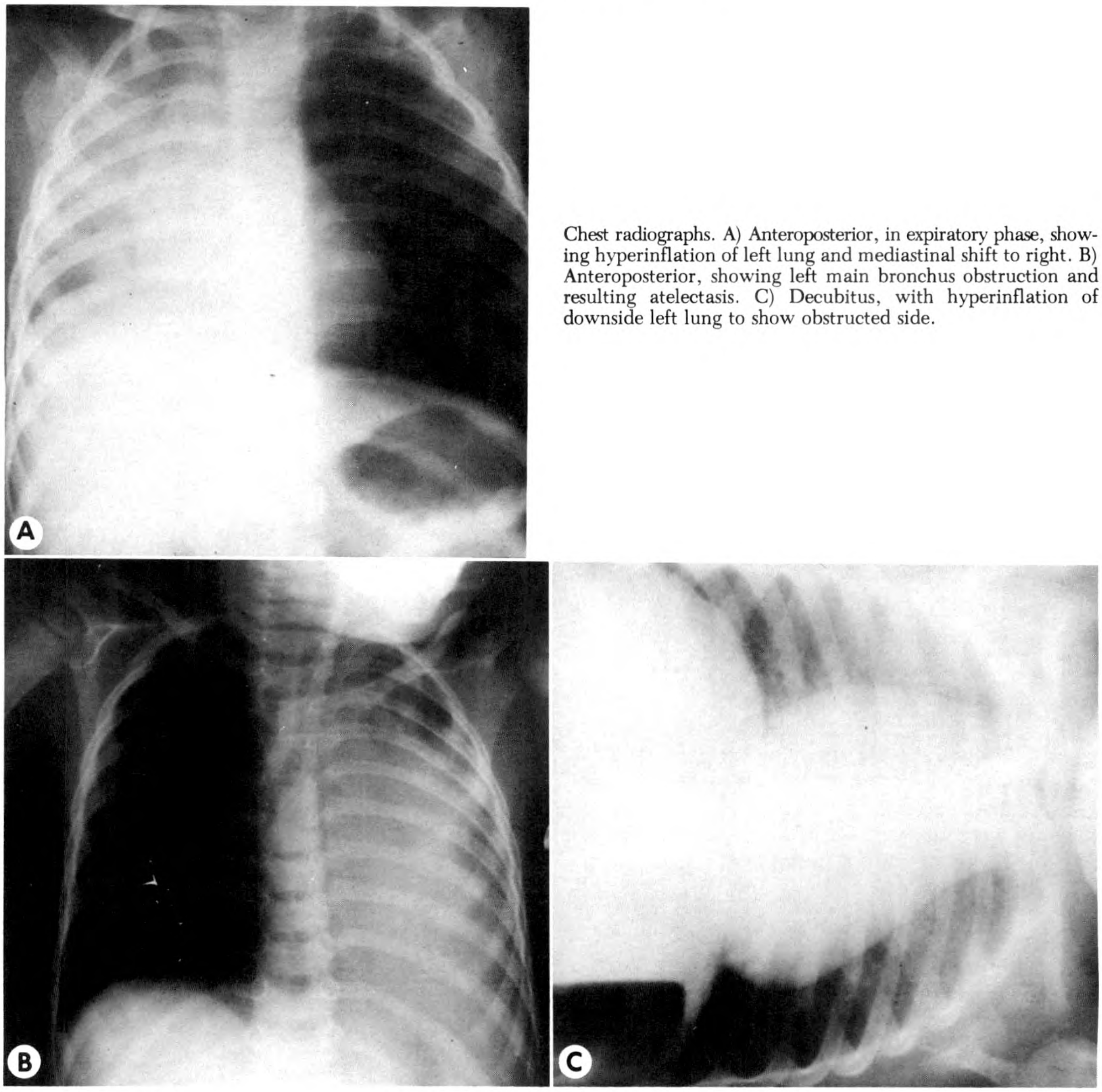
Presented at the meeting of the American Broncho-Esophagological Association, Palm Beach, Florida, May 2-3, 1990.



Chest radiographs. A) Anteroposterior, in expiratory phase, showing hyperinflation of left lung and mediastinal shift to right. B) Anteroposterior, showing left main bronchus obstruction and resulting atelectasis. C) Decubitus, with hyperinflation of downside left lung to show obstructed side.

diaphragmatic movement are compared on both sides of the chest, and obvious changes may point to the presence and location of a foreign object.

Both inspiratory and expiratory phase films should be obtained, and if fluoroscopy is not feasible, then decubitus films of the chest should be attempted. The "down side" of the chest will usually not empty on expiration if it is the involved side (see Figure, C).

Specific radiographic equipment such as the image intensifier may be used for foreign bodies that have migrated to the most peripheral portions of the lung. When used in conjunction with biplanar fluoroscopy, this equipment may be most helpful to the endoscopist.

EQUIPMENT

It is imperative that the endoscopist have a complete selection of appropriate endoscopes before attempting foreign body extraction. This would include a full range of rigid and flexible laryngoscopes, bronchoscopes, and esophagoscopes in sizes appropriate for both the neonate and the older child. The use of flexible endoscopes for foreign body removal in children, however, is limited by the lack of appropriate forceps.

A wide selection of extraction forceps must be available to the endoscopist, including peanut forceps, alligator forceps, ball bearing forceps, and tack forceps. Magnets of various sizes may also be useful in extracting metallic foreign objects. In addition, appropriate telescopes for magnification are quite useful in achieving better definition of the foreign body position and configuration.

Telescopic forceps have been a recent advance to aid the endoscopist in difficult foreign body extractions. They are ideally suited for teaching situations and provide an accurate means of extracting specific foreign bodies. Unfortunately, a large variety of forceps are not available, so their use is limited to some degree. In addition, the placement of a telescope in smaller bronchoscopes with the forceps attachment sometimes limits ventilation of the patient.

On occasion the Fogarty catheter has been employed to move impacted foreign bodies. This tool must be used with great caution, inasmuch as the balloon tip may break and become a second foreign object proximal to the impacted material.

MANAGEMENT

General Principles. Once the diagnosis of foreign body aspiration is suspected, the burden of proof of its presence or absence is on the endoscopist. A complete examination of the aerodigestive tract should be taken with the child under general anesthesia. Extraction with rigid instrumentation with control of the airway is still the method of choice.

Before any procedure is initiated, the endoscopist and anesthesiologist should carefully evaluate all pertinent radiographs, as well as the characteristics of the suspected foreign body. In this way, a proper plan of action can be implemented in an effort to avoid a crisis situation. The endoscopist should then survey all equipment that will be necessary for the procedure. If possible, an exact replica of the foreign body should be obtained so that appropriate extraction forceps can be selected.

The prevalence of the acquired immune deficiency syndrome requires that strict precautions be taken to protect both the endoscopist and surrounding operating room personnel. Strict sterilization protocols must also be observed in this regard.

Procedure. After a careful assessment and operative plan have been developed, the induction of general anesthesia begins. Manipulation is minimized and a slow, careful mask induction is undertaken until the patient reaches a satisfactory depth of anesthesia while still maintaining spontaneous respiration. An intravenous line is then placed, and the pharynx and larynx are topically anesthetized with 0.5% Xylocaine solution. An oximeter is used to monitor adequate ventilation.

Positioning is extremely important in ensuring both an adequate examination and the comfort of the endoscopist. The patient should be placed in the reverse Trendelenberg position to allow a direct, straight line of sight through the endoscope. A roll is placed under the shoulders, and the head is hyperextended. Care should be taken to protect the lips, teeth, and gingiva as the endoscopy proceeds. Eye protection is also provided.

An introducing laryngoscope is usually employed to inspect for the possibility of a foreign object in the larynx, as well as for the purpose of inserting a ventilating bronchoscope. A bronchoscope with a telescopic attachment is used to inspect the trachea and the bronchi with all subdivisions. After the foreign body has been located, the endoscopist must be careful not to engage in excessive manipulation that would dislodge the object and move it more peripherally. Careful examination of the object and its relationship to surrounding structures should be undertaken. At this point a decision is made as to whether the object may be extracted through the bronchoscope or is too large. In this case, it must be brought to the tip of the bronchoscope and then both the bronchoscope and the foreign body are extracted as a unit. The anesthesiologist must be alerted before the actual extraction takes place so that the patient's level of anesthesia is of sufficient depth to avoid laryngospasm as removal occurs. Once the object has been removed, a complete reinspection of the airway should be undertaken to rule out the possibility of a second foreign object. At this point many endoscopists will also inspect the esophagus to be certain that no object is present in that location as well.

Postoperatively, the patient is usually given antibiotics, and vigorous chest physiotherapy is undertaken for at least 48 hours to encourage expectoration of secretions. Humidification is also useful for this purpose.

Postoperative radiographs are usually obtained to ensure that full reexpansion of the lung has taken place and that no evidence of pneumothorax exists.

CONCLUSION

Sophistication in radiology, anesthesia, endoscopy equipment, and techniques should make the removal of foreign bodies from the aerodigestive system relatively safe and reliable for patients. This procedure should not be undertaken by the unskilled or occasional endoscopist. There are no shortcuts to the solution of these challenging clinical problems.

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Ann Otol Rhinol Laryngol 99:1990

NEW SET OF PEDIATRIC LARYNGOSCOPES

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With new advances in pediatric otolaryngology, the awareness of difficulties with existing laryngoscope instruments has become more apparent. The following paper introduces four new pediatric laryngoscopes for use in premature infants, the neonate and infant, the toddler-size child, and the preadolescent-size child. The reasons for the need of new laryngoscopes are explained, and the modifications to existing scopes that are currently employed are discussed. The need for continuous insufflation of oxygen during difficult as well as routine intubation is underscored with reference to the current anesthesia literature. Ventilating techniques in laryngoscopy for the non–respirator-dependent child are discussed.

KEY WORDS — children, laryngoscope, rechargeable portable light source.

Anesthetic techniques and surgical expertise have dramatically progressed over the last two decades in pediatric otolaryngology. The need for more versatile and sophisticated laryngoscopes appropriate for the size of our patients has become apparent. Current laryngoscopes available for use in children have specific limitations such as no incorporated method for the delivery of inhalational anesthetic agents and restricted visualization for instrumentation and laser therapy. Other problems encountered include awkward suspension and the laryngoscopes' not being adaptable to the widely variable sizes of children ranging from premature neonates through adolescents.

A new set of pediatric laryngoscopes was recently developed to encompass this spectrum of patients. They are available through Karl Storz (models 8576 C, 8576 D, and 8576 E) (Fig 1). An informal assessment was conducted at Wilford Hall US Air Force Medical Center of a wide variety of laryngoscopes from various manufacturers. The shortcomings of these other instruments helped to advance the design of the new laryngoscopes.

Children go through enormous physical changes from the neonatal period to adolescence. There cannot be a single laryngoscope designed that will fit all sizes of children comfortably and give unim-

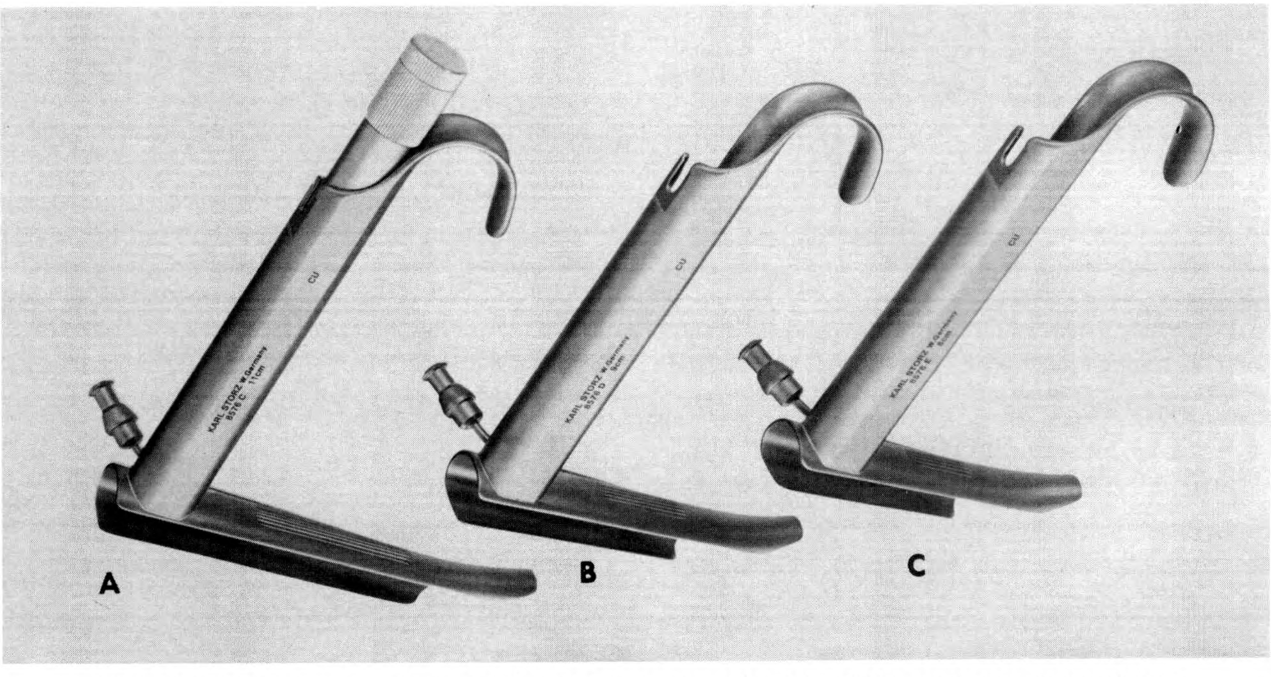

Fig 1. Pediatric laryngoscopes. A) For toddlers. B) For neonates and infants. C) For premature neonates. Largest scope (A) also demonstrates rechargeable portable prismatic light source.

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Presented at the meeting of the American Broncho-Esophagological Association, Palm Beach, Florida, May 2-3, 1990.

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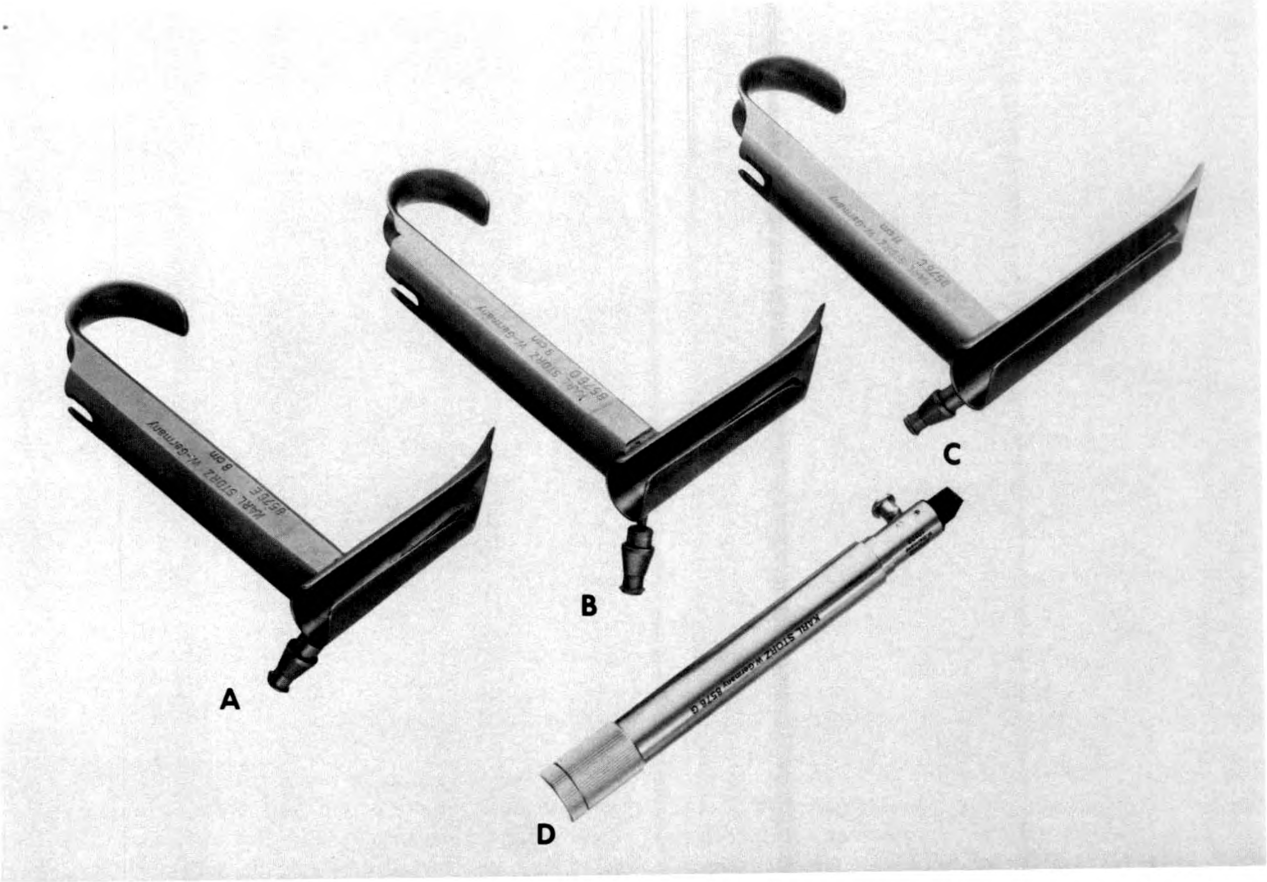

Fig 2. Three new pediatric laryngoscopes with side slits large enough to accept age-appropriate bronchoscopes or endotracheal tubes. A) For premature infants. B) For term newborns and infants. C) For toddlers. D) Rechargeable portable prismatic light source.

paired visualization. For this reason, three new laryngoscopes have been designed, one each for use in the premature infant, the neonate and infant, and the toddler. A fourth laryngoscope was modified from an existing design.

The purpose of this paper is to introduce several innovations for pediatric endoscopy, including this newly developed set of small pediatric laryngoscopes, a rechargeable portable light source (Figs 1 and 2), the modifications of an existing laryngoscope for larger children, and an improved suspension system (Fig 3). A discussion of the improvements created by these scopes is given.

One of the striking features of the hyoid in small children is its relative resistance to motion, as compared to that in adults, because of the short parahyoid musculature. This factor, combined with the high pediatric elevation of the larynx, makes the middle portion to base of the tongue mildly difficult to displace away from the surgeon with laryngoscope placement. The tongue then flops easily to the right or left of the laryngoscope. Such tongue asymmetry distorts the supraglottis. These new laryngoscopes are created with a flattened superior surface that is roughened so that the tongue will be supported during the insertion and held in place for the procedure. This support is particularly important when an open side slit is added to the scope so that the tongue does not rotate off the blade and into the lateral slit.

One of the characteristics of existing small laryngoscopes has been that the proximal viewing end (relative to the surgeon) has been approximately the same diameter as the distal end of the scope. These new laryngoscopes have a widened proximal end for enhanced binocular viewing that gives improved vision to the surgeon. This feature is particularly beneficial when instrumentation or a laser procedure is required.

The anterior commissure scope feature is well understood by most pediatric otolaryngologists and is incorporated into these newly developed scopes. As the larynx of the small child is more anterior and superior than that of the adolescent, a gradually increasing anterior commissure elevation is incorporated into each scope as the scopes get smaller.

It is reported in the anesthesia literature[1] that oxygen tension decreases during intubation in infants. When supplemental oxygen is used during the anesthesiologist's laryngoscopy for intubation, the mean drop in oxygen tension is 7 %, while without oxygen

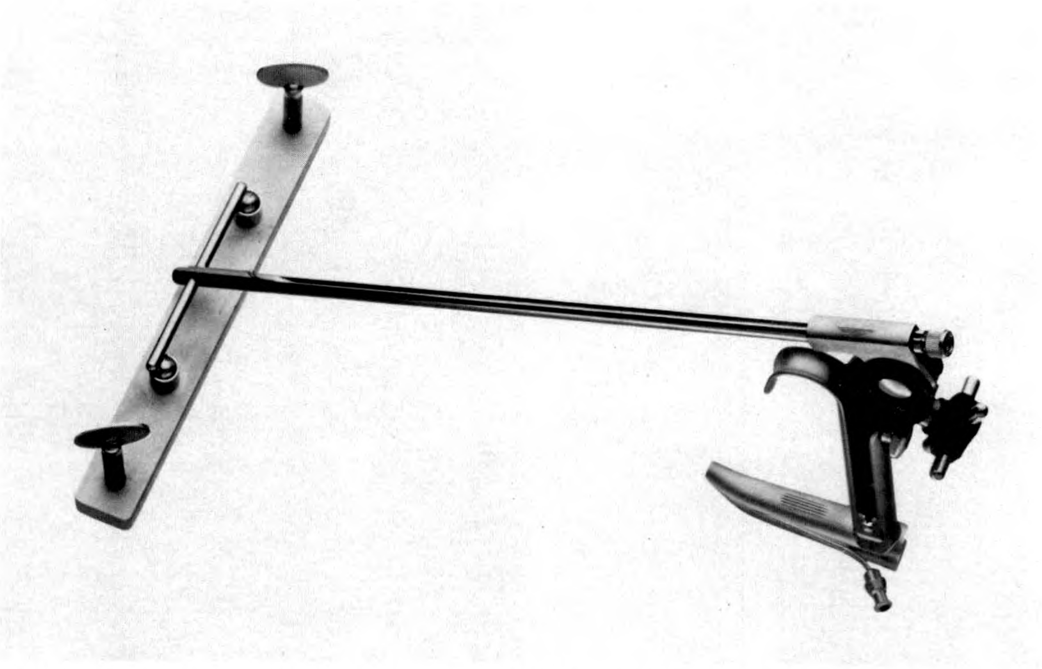

Fig 3. Modifications to existing suspension system. Pediatric suspension head is redesigned to allow it to fit on adult-length shaft. Chest support ring is replaced with flat bar with leveling screws.

supplementation the drop is 33%. In those children with an anatomically distorted airway, in whom intubation is more difficult, the oxygen tension drops even further. With these data in mind, we incorporated a side channel into each of these laryngoscopes so that oxygen insufflation or oxygen combined with an anesthetic gas can be given to the child during intubation or for prolonged laryngoscopic procedures. This side channel also can be used for jetting, as its distal opening is approximately at the level of the supraglottis.

The light source is delivered through the handle with a prism and is quite easy to place. It does not interfere with the vision of the surgeon and is quite adequate for all laryngoscopic procedures.

A side slit has been incorporated into the right side of the laryngoscope to enhance intubation and instrumentation. This slit makes the scope particularly beneficial for difficult intubations. It allows the endotracheal tube to be placed under optimal visualization, and the laryngoscope can then be removed. The slit also allows for angular instrumentation in such a fashion as to effectively increase the lateral dimensions of the proximal end of the scope to an even greater extent than is possible with an oval closed scope.

In respirator-dependent children, in whom an endotracheal tube is already in place before the procedure begins, the side slit allows the laryngoscope to be placed with adequate visualization of the vocal cords. The tube can then be removed through the scope without distortion of the supraglottic structures. When the artificial airway is removed in this manner, a short but thorough direct laryngoscopy can be performed and the child can be easily reintubated with a tube or bronchoscope. The side slit is wide enough to allow passage of the appropriate-size bronchoscope or esophagoscope.

All three of these laryngoscopes are suspendable and very amenable to laser endoscopy. The anesthetic techniques that can be used include spontaneous ventilation with insufflation of gases through the side channel, jetting using the same passage, intubation, or apnea.

The laryngoscopes were specifically designed to be light in weight without a large cumbersome handle that strikes the infant's chest. They are easily inserted and controlled with the smaller manageable handle.

Our experiences with these instruments have demonstrated a marked improvement in laryngoscopic procedures in small children and infants.

For children in the larger toddler through preadolescent ages, we modified the Benjamin pediatric laryngoscope[2] by removal of the right side channel, creation of a side slit, and roughening of the superior surface for improved support of the tongue. These alterations give greater flexibility to an already superb scope.

The suspension head for the Karl Storz pediatric chest support was modified to allow it to fit interchangeably on the adult suspension rod (Fig 3). The chest support was changed to a solid flat bar with lateral adjustment screws to give improved stability on the overtable and to remove the suspension from the patient's chest. These alterations make a more stable platform for pediatric suspension laryngoscopy.

A rechargeable, portable prismatic light source (model 8576 G) was developed to give more flexibility and adaptability to the three smaller laryngoscopes (Figs 1 and 2). This very effective light package gives the otolaryngologist greater speed and mobility in emergency situations and allows anesthesiologists and neonatologists to use the scopes for primary elective or emergency intubations.

CONCLUSION

These new laryngoscopes give greater dimension to the armamentarium of the otolaryngologist who cares for the airway in children. They are particularly beneficial to those surgeons who deal with problem airways in children ranging from premature-infant size through toddler size. The features of the laryngoscopes and the portable rechargeable light source also make them particularly amenable for use by anesthesiologists in the operating room and neonatologists and pediatricians in newborn nurseries.

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Ann Otol Rhinol Laryngol 99:1990

TRACHEOTOMY IN THE FIRST YEAR OF LIFE

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Much has been written concerning complications of pediatric tracheotomies, but few studies have reviewed the complication rates of tracheotomies performed in the first 12 months of life. We reviewed the records of 60 patients who underwent tracheotomy in the first year of life between 1976 and 1988. This study includes 30 full-term infants and 30 premature infants, 16 of whom were very low birth weight preterm infants (≤32 weeks' gestation and <1,500 g birth weight). Overall complication rates were 3% intraoperative, 13% early postoperative, and 38% late postoperative. The early postoperative complication rate in preterm infants was nearly double that of full-term infants. The late postoperative complication rate of patients undergoing tracheotomy for airway obstruction was more than double that of patients requiring tracheotomy for pulmonary indications. Duration of tracheotomy, however, was felt to be the most important factor in the development of a late postoperative complication.

KEY WORDS — complications, infants, intraoperative complications, low birth weight infants, newborns, postoperative complications, premature infants, tracheotomy.

INTRODUCTION

Tracheotomy in the pediatric patient has been associated with significant morbidity and mortality compared to that in adults.[1] Among pediatric patients, a higher complication rate has been noted to occur in infants, particularly premature infants.[2,3] Gestational age, age at tracheotomy, underlying medical problems, weight at time of tracheotomy, indication for tracheotomy, and previous intubation have all been correlated with complications of tracheotomy in infants and have been implicated as possible etiologic factors increasing complication rates.[1-6]

Although the literature is replete with reviews of complications of pediatric tracheotomies, few studies have concentrated on tracheotomies performed in the first 12 months of life. In order to focus on this special group of patients, we reviewed the charts of all children less than 1 year of age undergoing tracheotomy over a 13-year period, analyzing complication rates and identifying factors that related to complications.

MATERIAL AND METHODS

The charts of patients who underwent tracheotomy at less than 12 months of age at Tulane Medical Center and Ochsner Foundation Hospital between January 1976 and December 1988 were reviewed. The following data were extracted from these charts and analyzed: age; gestational age; gender; weight; indication for tracheotomy; significant comorbidities; outcome; intraoperative, early, and late postoperative complications; mortality; associated endoscopic and surgical procedures; and duration of tracheotomy. Duration of tracheotomy was defined as the number of days from placement of the tracheotomy tube to decannulation, death, or last follow-up date. Intraoperative complications were defined as those complications that occurred while the tracheotomy was being performed. Early postoperative complications were defined as those that occurred within the first 7 days after the operation; those occurring after 7 days were termed late postoperative complications. For analytic purposes, a scoring system was devised to rate patients according to their significant comorbidities. One point was given for any disease process affecting a major organ system and the general health of the patient. These scores were summed up to give a total score for each patient. These total scores were used in the analysis to give a gross estimate of the patient's general health or illness.

All tracheotomies were performed in the operating room by the otolaryngology or pediatric surgery services with the exception of one emergent tracheotomy performed in the delivery room by an unspecified physician. Operative technique varied according to the preference of the individual surgeon.

Statistical analysis was performed on all data with use of 2 x 2 and 2 x 3 χ^2 analysis where appropriate.

RESULTS

A total of 60 infants undergoing tracheotomy were included in this study. There were 32 boys and 28 girls. Thirty-three were white, 25 black, and 2 Oriental. The study group consisted of 30 full-term infants (≥37 weeks' gestational age) and 30 pre-

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Presented at the meeting of the American Laryngological Association, Palm Beach, Florida, April 28-29, 1990.

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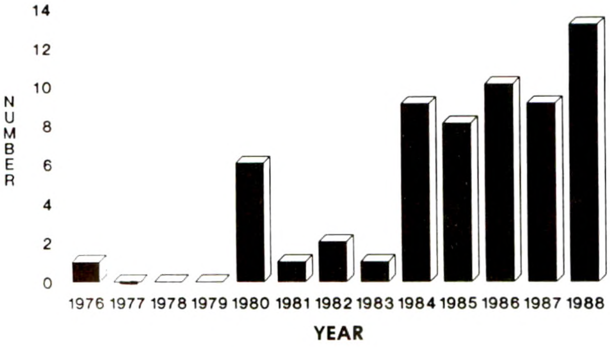

Fig 1. Infant tracheotomy by year performed. Number of tracheotomies performed has increased over past 13 years.

term infants (<37 weeks' gestational age), of whom 16 were very low birth weight preterm infants (≤32 weeks' gestational age and <1,500 g birth weight). The number of tracheotomies performed on infants per year increased steadily throughout the study period, resulting in a 13-fold increase from 1976 to 1988 (Fig 1).

Indications. Surgical indications were separated into three groups, including 1) upper airway obstruction (26 patients or 43%); 2) prolonged mechanical ventilation (31 patients or 52%); and 3) a requirement for another surgical procedure (3 patients or 5%) (Fig 2). Prolonged mechanical ventilation was an indication noted for patients in need of extended ventilatory support, a stable airway, and pulmonary toilet as defined by the primary care team. No standard policy regarding timing of tracheotomy was employed.

Comorbidity. The number and types of underlying medical problems were many and varied. The average comorbidity score for the entire study group was 3.6, ranging from 0 to 7. Table 1 contains the average comorbidity score according to gestational category, indication, and eventual outcome. Higher comorbidity scores were noted in preterm infants, patients that died, and patients requiring a tracheotomy for ventilator dependence.

Outcome and Morbidity. Among the 60 patients in the study group, 19 (32%) were still intubated at last follow-up, 16 (27%) were eventually decannulated, and 25 (42%) died with the tracheotomy tube in place. However, only one death was attributed to the tracheotomy, resulting in a 1.6% tracheotomy-related mortality rate; the other 24 patients died of their underlying medical problems. All deaths occurred in the hospital with the exception of the tracheotomy death occurring at home. Table 2 and Fig 3 summarize outcome as it is related to weight at time of tracheotomy, surgical indication, comorbidity score, and gestational category. Sixty-four percent of the patients weighing less than 3,000 g at the time of the tracheotomy died, and only one patient was decannulated. However, patients weighing greater than 3,000 g were decannulated in nearly 40% of the cases and only 29% died (p<.01). The mortality rate for patients

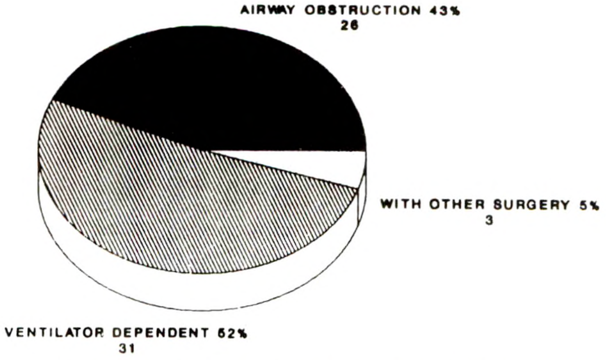

Fig 2. Distribution of indications for tracheotomy.

TABLE 1. MEAN COMORBIDITY SCORES FOR EACH SUBGROUP OF GESTATIONAL CATEGORY, SURGICAL INDICATION, AND EVENTUAL OUTCOME

	Mean (N)
Gestational category	
Full-term	3.0 (30)
Preterm	4.1 (30)
Very low birth weight preterm	4.3 (16)
Surgical indication	
Airway obstruction	2.8 (26)
Ventilator dependence	4.2 (31)
Associated with another procedure	2.3 (3)
Outcome	
Dead	4.2 (25)
Still intubated	3.1 (19)
Decannulated	2.4 (16)

TABLE 2. OUTCOME PRESENTED AS SUBGROUPS OF WEIGHT AT TRACHEOTOMY, SURGICAL INDICATION, COMORBIDITY SCORE, AND GESTATIONAL CATEGORY

		Dead		*Decannulated*		*Still Intubated*	
	N	*No.*	*%*	*No.*	*%*	*No.*	*%*
Weight at tracheotomy							
<3,000 g	22	14	64	1	5	7	32
≥3,000 g	34	10	29	13	38	11	32
Unknown	4	1		2		1	
Indication							
Airway obstruction	26	7	27	9	35	10	38
Ventilator dependence	31	17	55	5	16	9	29
Prerequisite for other operations	3	1		2		0	
Comorbidity score							
0-3	30	8	27	11	37	11	37
4-7	30	17	57	5	17	8	27
Gestation							
Full-term	30	7	23	13	43	10	33
Preterm	30	18	60	3	10	9	30
Very low birth weight preterm	16	9	56	2	13	5	31
Total	60	25	42	16	27	19	32

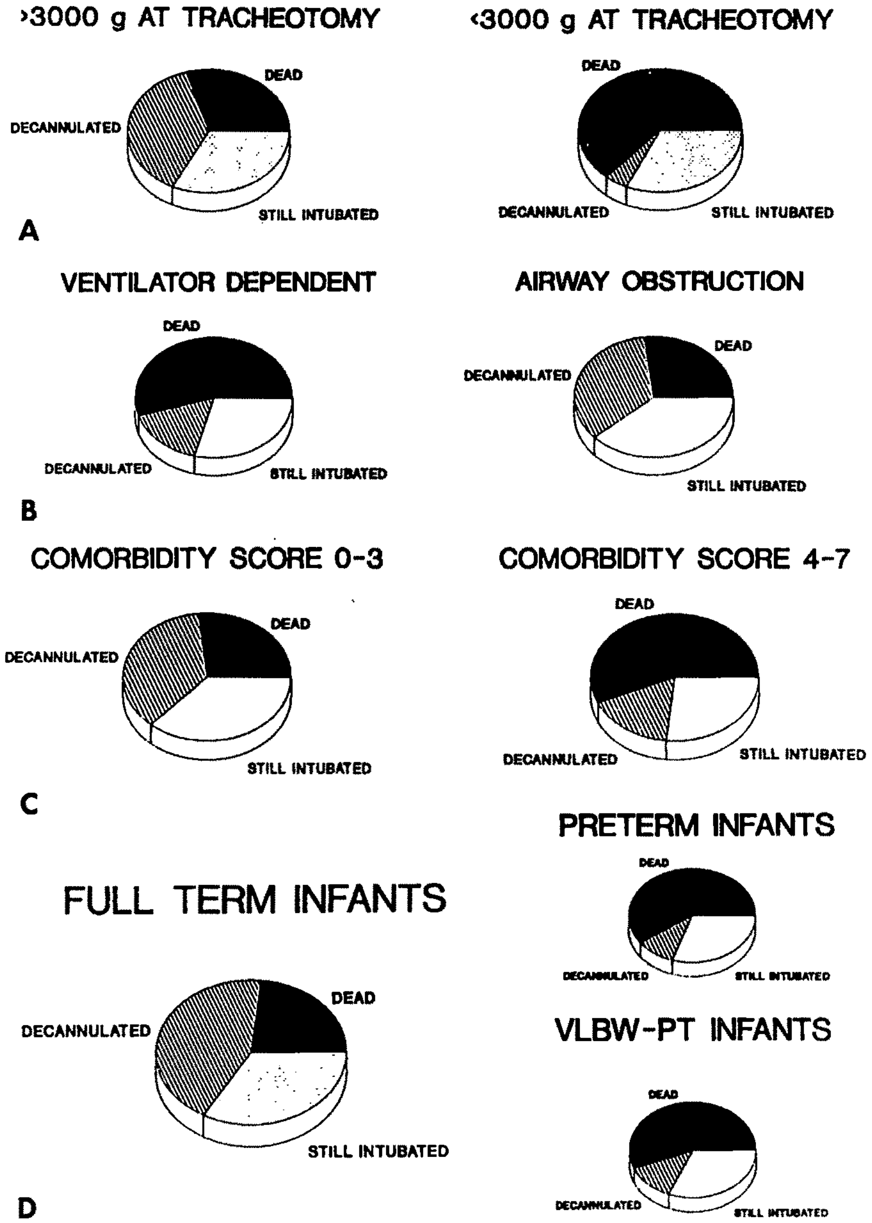

Fig 3. Outcome distributions related to A) patient weight at time of tracheotomy, B) indication for tracheotomy, C) patient comorbidity scores, and D) patient gestational category.

requiring tracheotomy for prolonged ventilation was double that for patients undergoing tracheotomy for airway obstruction, and the former were half as likely to be decannulated. Likewise, patients with comorbidity scores greater than 3 were twice as likely to die and half as likely to be decannulated as those with comorbidity scores of 3 or less. Twice as many full-term infants survived and four times as many were decannulated compared to preterm and very low birth weight preterm infants ($p<.05$). Among the 19 patients still intubated, only one had attempts at decannulation at the time of this study.

Other Procedures. Nearly one third of the patients underwent other types of airway operations (32 surgical procedures in 18 patients). Twenty-two of these procedures were done in an attempt to avoid tracheotomy or hasten decannulation, including anterior cricoid split (3), tracheal dilation (11), glossopexy (2), carbon dioxide laser excision of subglottic hemangioma (2), laryngotracheoplasty (2), and other, minor procedures (2). Thirty-three patients underwent 48 endoscopic procedures (1.5 procedures per patient) prior to tracheotomy, and 28 patients underwent 59 endoscopic procedures (2.1 procedures per patient) after tracheotomy. Fifteen patients required 20 procedures for removal of granulation tissue prior to decannulation.

Follow-up. Mean follow-up time after tracheotomy was 301 days (range, 1 to 2,247 days). The average survival for patients who died was 88 days. The mean follow-up of patients eventually decannulated was 535 days, and of patients still intubated at their last follow-up examinations, 298 days. The average follow-up was 545 days for patients with airway obstruction as the indication for tracheotomy, and 122 days for patients with prolonged ven-

TABLE 3. NUMBER AND TYPE OF COMPLICATIONS

Complication	*No.*
Intraoperative	
Tracheal tear	1
Bilateral pneumothorax	1
Cricothyroid intubation	1
Total (3.3% of patients or 2)	3
Early postoperative	
Tube obstruction	5
Pulmonary edema	1
Sepsis	1
Atelectasis	1
Pneumomediastinum	1
Total (13.3% of patients or 8)	9
Late postoperative	
Granulation tissue	15
Obstructed tube	7
Tracheitis	2
Accidental decannulation	2
Tracheal stenosis	2
Tracheomalacia	2
Bleeding	1
Skin breakdown	1
Aspiration	1
Total (38.3% of patients or 23)	33

TABLE 4. COMPLICATION RATES ACCORDING TO GESTATIONAL GROUP, INDICATION, COMORBIDITY SCORE, AND DURATION OF TRACHEOTOMY

		Operative		*Early*		*Late*	
	N	*No.*	*%*	*No.*	*%*	*No.*	*%*
Gestational group							
Full-term	30	1	3	3	10	11	37
Preterm	30	1	3	5	17	12	40
Very low birth weight preterm	16	0		3	19	7	44
Indication							
Airway obstruction	26	2	8	4	15	14	54
Ventilator dependence	31	0		4	13	7	23
Prerequisite for other operations	3	0		0		2	
Comorbidity score							
0-3	30	1	3	5	17	15	50
4-7	30	1	3	3	10	8	27
Duration							
0-100 days	28	2	7	2	7	3	11
101-500 days	22	0		2	9	12	55
>500 days	10	0		4	40	8	80
Total	60	2	3.3	8	13.3	23	38.3

tilation. Full-term patients averaged 390 days of follow-up, compared to 212 days of follow-up in the preterm infants. These large variations in follow-up time were mainly due to higher mortality rates among the prolonged ventilation and preterm groups.

Complications. Tables 3 and 4 and Fig 4 summarize the complications of tracheotomy. Only two patients (3.3%) encountered intraoperative complications. One patient underwent emergency cricothyrotomy in the delivery room for congenital laryngeal obstruction resulting in bilateral pneumothoraces requiring bilateral thoracostomy tube placement and subsequent repair of the cricothyroid membrane defect. The other patient suffered a tracheal tear while undergoing concomitant tracheotomy and tracheal dilation.

Eight patients had nine complications within the first postoperative week, for a 13.3% early postoperative complication rate. The most common complication in the early postoperative group was tracheotomy tube obstruction (five patients) causing respiratory distress. One patient with tube obstruction and severe respiratory distress on the first postoperative day had his tube changed by the intensive care staff, and this action created a false tract and a pneumomediastinum. Stay sutures were employed in this patient and aided in the correct replacement of the tracheotomy tube by the otolaryngology staff. The pneumomediastinum resolved with expectant management. An 11-month-old infant with chronic upper airway obstruction developed pulmonary edema after relief of the obstruction with tracheotomy.

Twenty-three patients (38.3%) developed 33 late postoperative complications. The most common of these was significant intraluminal granulation tissue requiring removal (15 patients). Intraluminal granulation tissue is a common if not universal finding in the tracheotomized patient; however, this was only considered a complication if it required therapy (ie, removal). The second most common complication was tube obstruction (7 patients), resulting in cardiopulmonary arrest in 2 patients and severe respiratory distress in 5 patients. Accidental decannulation, tracheitis, tracheal stenosis, and tracheomalacia each occurred twice. Skin breakdown around the tracheotomy site, significant bleeding that resolved spontaneously, and aspiration after vomiting onto the tracheotomy site each occurred once.

There was only one tracheotomy-related death (1.6%). This child became decannulated accidentally while unobserved at home 1 year postoperatively.

Nearly twice as many preterm infants encountered early postoperative complications as compared to full-term infants. Similarly, almost twice as many early and late postoperative complications occurred in patients with lower comorbidity scores. Patients requiring tracheotomy for airway obstruction had more than twice as many late postoperative complications as patients whose tracheotomy was performed for ventilator dependence ($p < .02$). A directly proportional relationship existed between the duration of the tracheotomy and the number of patients with late postoperative complications:

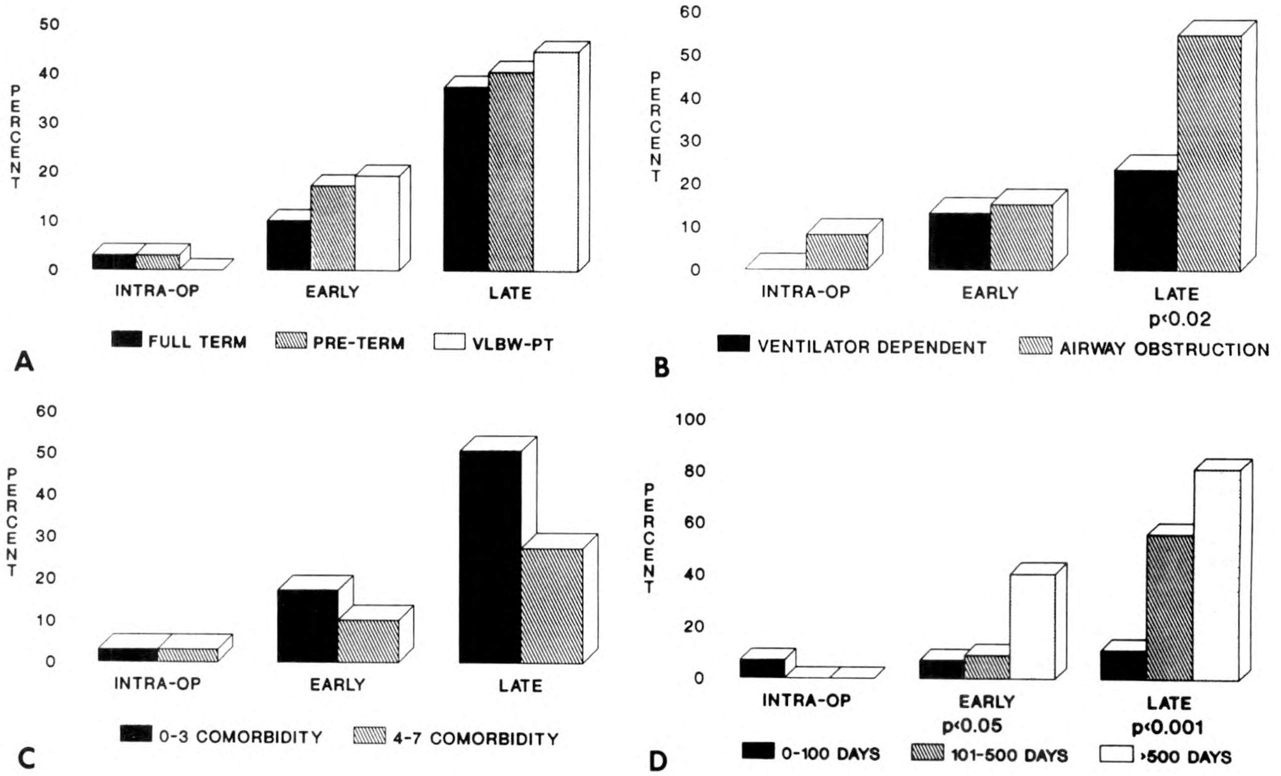

Fig 4. Complication rates by A) gestational category, B) indication for tracheotomy, C) comorbidity score, and D) duration of tracheotomy.

11% for patients with the tracheotomy in place for less than 100 days, 55% for 101 to 500 days, and 80% for greater than 500 days ($p<.001$).

DISCUSSION

The number of tracheotomies performed per year has increased over the past few years, reflecting the improved care provided in modern neonatal intensive care units. These neonates tend to be smaller and more critically ill.

There have been very few reports in the literature specifically reviewing tracheotomy in patients less than 1 year of age. Mortality from the procedure itself ranges from 0% to 4.6%.[2,5,7,8] This rate compares favorably to our experience of 1.6% and demonstrates that tracheotomy in the very young, although not a totally benign procedure, can be performed relatively safely by experienced surgeons on even the smallest of patients. However, the overall mortality of this group of patients is very high and was 42% in our series compared to a reported range of 25% to 75%.[2,5,7,8] This rate indicates that tracheotomy is generally reserved for the most seriously ill infants.

Our comorbidity scoring system was devised to quantify the severity of the child's overall state of health or illness. It is clear from our data that the higher the comorbidity score a patient has, the worse the prognosis for decannulation and also survival. There was an inverse relationship between the comorbidity score and the number of both early and late postoperative complications. This outcome can be best explained by the fact that the more severely ill patients died of their other illnesses, whereas the healthier children survived for a much longer period of time. It is apparent from our data as well as those of others that the longer a patient has a tracheotomy, the more tracheotomy-related complications will occur.

We concur with the findings of Kenna et al[2] of a much higher complication rate among preterm patients than among full-term (48% versus 24%). Wetmore et al[6] reported the highest complication rates among patients requiring tracheotomy for upper airway obstruction — also in agreement with our data. However, the reason for this apparent correlation is not based on the indication for the tracheotomy, but rather the fact that patients who undergo tracheotomy for upper airway obstruction survive longer than patients who have a tracheotomy tube placed because of ventilator dependence (545 days versus 122 days) and therefore have more of an opportunity for complications.

Significant mortality rates (25% to 75%) have been reported in children less than 1 year of age who undergo tracheotomy.[2,5,7,8] However, these reports have not reviewed other procedures these patients have undergone or may need in the future. Our data show that 18 patients underwent 32 nonendoscopic upper airway procedures in addition to the tracheotomy. Also, 48 endoscopies were performed on 33 of the patients prior to tracheotomy and 59 endoscopies were performed on 28 patients following tracheotomy. Fifteen patients underwent 20 procedures for removal of granulation tissue prior to decannulation.

Several authors have commented on the difficulty of decannulating patients once the need for the tracheotomy tube has been eliminated. This has not been our experience. This difference may be attributable to routine endoscopy to excise granulation tissue prior to tracheotomy removal and gradual reduction in tracheotomy tube size, which is similar to the technique suggested by Willis et al.[9]

Emergency tracheotomy without a controlled airway is associated with significant intraoperative complications. Indeed, the only patient in our series who had an emergency tracheotomy accounts for two thirds of our intraoperative complications. This occurrence underscores the need for a controlled airway prior to tracheotomy, as recommended by many other authors.[1-8,10-12]

Our experience clearly indicates a direct, linear relationship between duration of tracheotomy and late postoperative complications. This correlation reinforces the need for close follow-up, decannulation as early as possible, periodic endoscopic examinations when indicated, extensive training of family members, and a coordinated team approach including otolaryngologic, pediatric, nursing, and social service personnel.

CONCLUSIONS

1. Infant tracheotomy is characterized by very high overall mortality rates (42%) but very low tracheotomy-related mortality rates (1.6%), a low rate of intraoperative complications (3.3%), an intermediate rate of early postoperative complications (13.3%), and a high rate of late postoperative complications (38.3%). In this study, the most common early complication was tube obstruction, and the most common late complication was intraluminal granulation tissue.

2. A direct linear relationship was found between the number of late postoperative complications and duration of tracheotomy. Duration of tracheotomy was felt to be the most important factor affecting late complication rates.

3. A dramatic rise in the number of infant tracheotomies performed per year at our institutions was found over the 13-year study period. This rise may be a reflection of increased survival of neonatal intensive care unit patients.

4. Emergency tracheotomy in a neonate or infant is a hazardous undertaking, and other methods of initially establishing an airway are preferred if feasible.

5. Close and intensive follow-up for the entire duration of tracheotomy is imperative.

6. Higher comorbidity scores did not correlate statistically with higher complication rates in this study.

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SYSTEMS ARCHITECTURE FOR QUANTIFICATION OF DYNAMIC MYOELECTRIC AND KINEMATIC ACTIVITY OF THE HUMAN VOCAL TRACT

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This paper describes a systems architecture useful for scientific investigations that require the acquisition and analysis of multiple, time-synchronous signals in large volume. The architecture has recently been developed by this group to enhance our capability to research and quantify central nervous system function in the production of normal and pathologic speech. The architecture utilizes modern advances in desktop microcomputers and has been designed so that vocal motor control laboratories (or similar settings) with modest funding can more fully participate in comprehensive investigations of speech production. Research experiments organized with this architecture may involve many more subjects and measures than previously possible without significant increases in time and personnel resources. This paper will demonstrate the technique and practicality of this architecture as it is being used to successfully guide research to map hierarchic central nervous system regions of involvement in two speech disorders: spasmodic dysphonia and stuttering. The architecture has broad usefulness to many areas of otolaryngology and health science.

KEY WORDS — computers, data acquisition, data analysis, speech pathology, speech production.

INTRODUCTION

Speech production is a highly skilled and complex action involving simultaneous activation of multiple physiologic mechanisms. Consequently, comprehensive investigation of the speech motor system requires the ability to acquire and analyze multiple physiologic signals in an efficient and organized manner. Modern endeavors to more fully understand the speech motor system and its control by the central nervous system continue to encourage the following directives.[1]

1. To investigate the many concurrent myoelectric, aerodynamic, and kinematic components involved in production of the speech acoustic signal and, inasmuch as possible, to study these components and their interactions as they occur *simultaneously*.
2. To acquire these component signals for a broad spectrum of speech and vegetative tasks that exercise specific aspects of speech motor system physiology and central nervous system involvement.
3. To compare multiple tokens (samples) of data among many normal and pathologic subjects, leading to quantification of the component activities.

Because of the overwhelming complexity of these tasks and the enormous volume of data required to attain these directives, most laryngologists and speech researchers are without the essential means to thoroughly investigate normal and pathologic speech production. Few researchers have attempted to simultaneously acquire and assess more than a few correlates of speech motor system activity, and when they have, it is usually among a few subjects or with emphasis on a specific physiologic component such as aerodynamic-acoustic or vocal fold kinematic–acoustic ones. Notable exceptions are two or three well-funded laboratories adequately equipped with large mainframe computer systems and support personnel to partially accomplish these objectives along lines coincident with their current research prerogatives. It is not unusual for only 30 minutes of multiple-channel recorded speech tasks to result in over 100 million bytes of digitized data for a single subject. (By comparison, the first desktop microcomputer issued by IBM Corporation in 1981 stored and accessed a total of 200 thousand bytes of digital data.[2]) Consequently, quantification of the speech motor system during normal and disordered speech remains, for the most part, inadequately understood by laryngologists and speech scientists alike.

Accelerated advances in the microcomputer electronics industry have made it possible to place onto

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Presented at the meeting of the American Laryngological Association, Palm Beach, Florida, April 28-29, 1990.

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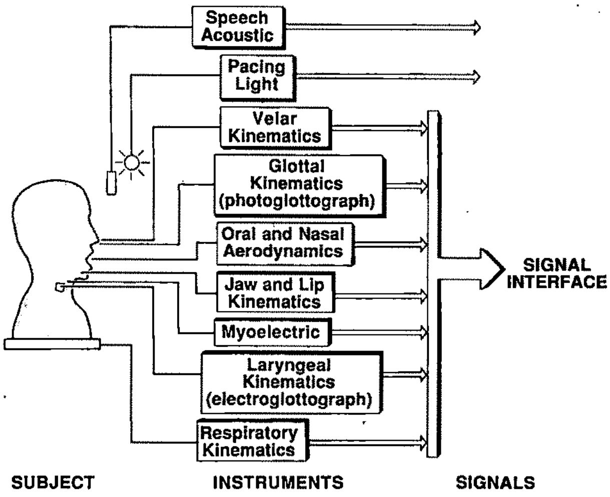

Fig 1. Schematic of multiple myoelectric, kinematic, aerodynamic, and acoustic signals from speech motor system acquired during typical experimental session.

the desktop of every medical researcher the ability to economically perform signal input and analysis tasks equivalent, for example, to that achieved by the sophisticated *Galileo* space probe, launched by the United States in 1990. However, utilization of these powerful, dedicated microcomputer systems and their sophisticated peripheral devices (such as the optical laser disk) has not been developed in the health sciences in ways equivalent to that in many other research and industrial environments. The successful development of such computer-automated systems for health science research and clinical applications requires the skillful interaction of multiple scientific disciplines, including laryngologists, speech scientists, electrical engineers, and computer scientists. For the research or clinical laryngologist, such a microcomputer-based architecture should do the following.

1. Provide a cost-efficient means to comprehensively investigate speech motor system activity (as discussed in a previous paragraph), including the ability to accommodate multiple physiologic signals, generate experimental task protocol lists, organize control of the data acquisition session, maintain data-base records of acquisition and analysis activity, interface to acquisition and recording instruments, monitor real-time acquisition of signals, calibrate signal data to actual units, perform powerful digital signal processing, and provide complete organization and easy access to data during input, storage, analysis, and graphic output.
2. Be easily configurable to other similar research and clinical tasks by the end-user.
3. Provide a convenient, standardized format for the sharing of data and applications among laboratories.

This paper describes a microcomputer-based systems architecture with all of the aforementioned essentials. Future papers by this group will report quantitative results obtained from applications of this architecture to current research.

METHODOLOGY

Speech Motor System Measures. Figure 1 depicts the investigation of multiple myoelectric, kinematic, and aerodynamic components of the speech motor system in a typical experimental session. Each physiologic component of interest is measured with precision laboratory instruments that provide voltage waveforms to the signal interface representative of the specific physiologic activity. Particulars of speech motor system instrumentation have been the topic of numerous papers, and many notable advances continue to be made.[3,4] This paper will devote itself to the computer-assisted system that acquires, organizes, and analyzes the multiple signals made available to the signal interface shown in Fig 1.

A typical experimental session might be dedicated to acquiring five myoelectric signals, two laryngeal kinematic signals, one velar kinematic signal, one jaw kinematic signal, and two lip kinematic signals. Accompanying these physiologic signals are one or more time-synchronous speech acoustic signals obtained from carefully positioned microphones. The signal controlling the pacing light is produced by the computer system as part of its over-

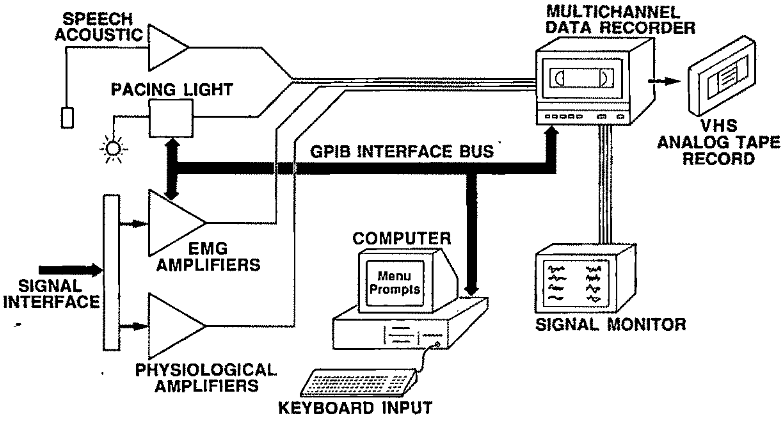

Fig 2. Block diagram of microcomputer-based acquisition and monitoring component of systems architecture.

TABLE 1. DESCRIPTION OF SYSTEM COMPONENTS

Computer	Compaq 386 25 MHz; 300-megabyte fixed disk; 80387 math coprocessor; VGA 19-in color graphics monitor; this workstation is implementable with any IBM AT–type computer
GPIB interface	IO Tech Personal 488 (IEEE-488 format)
Signal interface	Custom designed by group; 12 channels; gain/attenuation and baseline adjustment; precision calibrated; provides multichannel signal routing during acquisition, monitoring, and digitization
Processing board	Data Translation DT 2821-F-16SE; 16 channels; 12-bit resolution; 150-kHz maximum throughput sampling rate
Data recorder	TEAC XR-510WB VHS cassette data recorder; VHS analog tape format; 14 channels; FM-coded physiologic channels; direct wideband speech acoustic channels; GPIB interface; servo control; many types of data recorders applicable, including precision digital formats
Electromyographic amplifiers (8)	Human Performance Measurements, Inc; GPIB interface; differential-input, 8-position high-pass filter; 256-position seventh-order low-pass filter; 18-position gain adjust (100 to 256,000); 256-position baseline adjust; 45-dB 60-Hz selectable notch filter
Mass storage	Optimem 5.25-in optical WORM (write-once read many) disk drive unit; 660-megabyte capacity per disk
Signal monitor	IBM AT computer with 12-in color monitor; DATAQ Instruments and Keithly 570 oscilloscope interface
Software	Computer programs developed by the authors; also DSP Development Corp

all duty to organize the experimental session and is made available to the signal interface to provide identifying landmarks for time-sensitive tasks such as reaction-time and rate-control tasks.[5] Otherwise, the pacing light signifies that the recording instruments are prepared and that the subject may proceed to perform the specified task at a comfortable pace.

Signal Acquisition Microcomputer Work Station. A block diagram of the computer-assisted acquisition system is shown in Fig 2. Components of the system are detailed in Table 1. Central to the acquisition work station is the system controller: a high-speed 32-bit desktop computer. Modern desktop computers, equipped with generous hardware and software support, provide an ideal format for achieving the desired objectives and, in fact, offer many advantages over more expensive mainframe computers.

Operating under the software program ACQUIRE, the central computer controls peripheral devices and instruments via the industry-standard, general-purpose interface bus (GPIB).[6] The hierarchic structure of the menu-based software program ACQUIRE is detailed in Fig 3. Multiple signals from the signal interface (described in Fig 1) are recorded onto a magnetic tape cartridge by the multichannel data recorder in start-stop sequences. The acquisition session is automated by the system computer operating under the ACQUIRE program, thus permitting investigators to concentrate on subject performance and integrity of data collection.

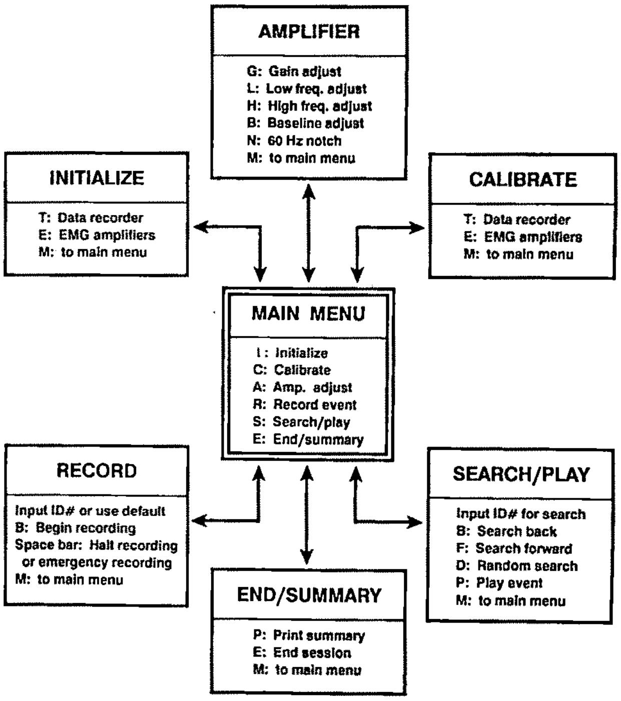

Fig 3. Illustration of menu-based software programs demonstrating user-friendly interface to systems architecture.

Guided by the computer-controlled pacing light, subjects perform a series of vegetative, linguistic, paralinguistic, rate-control, and reaction-time tasks that are identified by a unique session, task, and token code accompanying the recorded data. Automatic indexing with a numeric code facilitates all steps of post-session processing: tape playback, digitization, display, and analysis. The coding scheme for recorded data is described in Table 2, which also illustrates an example code for one token of the vocal task /sma/. A printed copy of the experimental task protocol is provided by the system computer at the beginning of each session according to the particular session number or study code. Task-type groups (eg, Vegetative, Linguistic, Reaction-time, etc) and tasks within groups (eg, ***hat***, /i/, ***oscar***) may be listed in random fashion if desired.

TABLE 2. DESCRIPTION OF DATA CODING

Code	*Description*	*Range*
a bb	Subject number	101 to 199 (controls) 201 to 299 (patients)
c	Repetition number	1 to 9
d	Session number	1 to 9
ee	Task number	00 to 99
f	Token number	1 to 9
g	File code	A to Z
h	Channel number	1 to 9, A to F
i	Edit number	1 to 9

Coding format is *a bb c d ee f . g h i.*

Example: For subject number 103, repetition number 1, session number 1, task code for /sma/ 12, token number 1, file code S (eg, binary sequential file), signal interface channel number 1, edit number 1 (ie, unedited version), then disk operating system file code is 10311121.S11. Inclusion of additional alphabetical characters extends each code category.

The acquisition work station is designed so that an experimental session may be conducted by two investigators: 1) a laryngologist who is attentive to the subject and describes the next task target and 2) a system operator at the computer keyboard who responds to user-friendly prompts from the software program. The session is easily managed by a single investigator conducting a noninvasive protocol.

The following sequence illustrates the process for acquiring one token of the vocal task /sma/. At the main menu level of the program hierarchy illustrated in Fig 3, the system operator presses R at the keyboard interface to activate the Record submenu. The Record submenu prompts the operator with "Next Task Number?" and "Token Number?" to which the system operator responds by entering the numbers 12 and 1, respectively (as numerically coded by the example in Table 2). The computer system interprets this task for the current session as being a member of the Linguistic group. The work station is idle until the operator begins the acquisition process by pressing B, at which time instructions are sent 1) via the GPIB to activate the multichannel tape recorder to proceed recording and 2) after a short delay, to the pacing light to signify that the subject may proceed. Upon completion of the task, which may be a single vocalization of /sma/ or a specified number of repetitions (eg, five repetitions of /sma/ on a single breath), the system operator presses the space bar to stop the tape recorder and return the system to the idle mode in the Record submenu. Subsequent tokens of task number 12 (that is, tokens 2, 3, 4, etc) are recorded as stop-start sequences on the tape by alternating B and space bar responses by the operator, before the system is returned to the main menu by pressing M. Each stop-start sequence is uniquely coded and typically is from a few seconds' duration to a few minutes, depending on the particular task and acquisition intent.

Acquisition instruments designed to accommodate the GPIB connection may be remotely controlled by the central computer as part of the acquisition protocol. For the system illustrated in Fig 2, the eight electromyographic amplifiers are controlled entirely by instructions received from the central computer via the GPIB interface. Likewise, acquisition instruments may send instructions along the GPIB notifying the central computer of an appreciable change in signal integrity or activity, which may in turn require an adjustment of instrument gain, bandwidth, noise rejection, baseline, and/or adjustment of recording electrodes or transducers. Under this framework, the experimental session is interactive while having the advantage of being centrally controlled. All waveforms from the signal interface are made visually available to the system operator throughout the acquisition session by a multichannel real-time monitor, as illustrated in Fig 2 and described in Table 1. Because some experimental sessions involve multiple endolaryngeal bipolar hooked-wire electrodes and various other invasive transducers, an interactive acquisition system is essential to minimize collection errors and potential loss of data.

Data Conversion and Calibration. Experimental data are converted into a form more convenient for analysis after the acquisition session has been completed. The multichannel signal data recorded onto a magnetic tape cartridge are converted into digital form and stored onto mass-storage media of the controlling computer. Following the guidelines given in Table 2, digitized data files are uniquely named by the disk operating system (DOS) according to the numeric code that accompanies the raw data. This process is completely automated by the software program CONVERT, which controls the tape recorder in the playback mode via the GPIB.

Digital files are converted to calibrated units (when appropriate) with an automated process during the intermediate processing stage. For example, all myoelectric data are converted to absolute values in microvolts, kinematic accelerometer data are converted to gram-meter per second per second, aerodynamic airflow data are converted to milliliters per second, etc. Calibration gain-, baseline-, and phase-adjustment factors for each channel are obtained from uniquely coded sequences on the tape cartridge that identify precision-referenced events recorded during the acquisition session. Once the data are calibrated, subsequent access and analysis will yield absolute instead of relative measures.

As the final step of data preparation, the calibrated data are stored onto write-once read-many (WORM) optical disk media. This state-of-the-art peripheral device is ideally suited to mass storage of physiologic data and has only recently been reliably adapted for use with desktop microcomputers. The WORM optical media provide 1) compact, convenient, and portable storage of all experimental data records; 2) fast, random access to all data files with the ability to append new data; and 3) high durability, low volatility, and an excellent expected lifetime. Since WORM media are nonerasable, careless use of the computer DOS (which might erase magnetic disk media) will not affect the experimental data. Once stored onto WORM optical media, data are unalterable and ready for future access.

By use of the example given in the footnote of Table 2, the stop-start sequence that recorded the first token of the task /sma/ for channel 1 of the signal interface is identified by the 11-character DOS code name 10311121.S11 on the WORM media. Data on the WORM media are available for random access to achieve playback, graphic output, or digital signal processing to extract relevant mea-

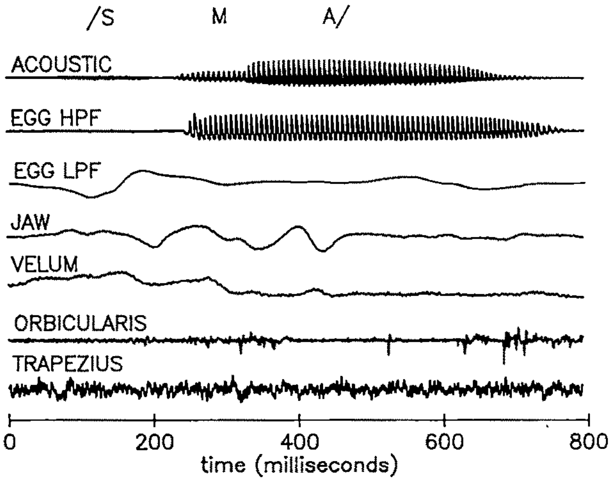

Fig 4. Multiple time-synchronous signals for one token of vocal task /sma/ by normal subject. EGG HPF — electroglottograph signal high-pass filtered at 40 Hz, EGG LPF — electroglottograph signal low-pass filtered at 26 Hz.

sures and quantify speech motor system activity. Accompanying the experimental data files on the WORM media are records of the acquisition and processing activity, which have been maintained by the computer work station.

RESULTS

Our current research application of this systems architecture (grant name *Vocal Tract Neuromotor Activity in Spasmodic Dysphonia*) includes 15 patient and 10 control subjects attending four 2-hour data acquisition sessions. During a single session, recording 10 signals from a single subject performing 400 vocal and vegetative tokens will result in approximately 160 million bytes of digital data contained in 4,000 individually coded files on the optical storage medium. Without this systems architecture in place to organize data acquisition and processing, such a comprehensive investigation of the speech motor system would require enormous time, money, and personnel resources. In the past, experimental protocols such as this have been limited to fewer subjects and many fewer tokens and are inherently restricted to consider only a few of the many potentially meaningful parameterizations of the raw signals.

Figure 4 illustrates a time-synchronous display of seven waveforms obtained with the computer work station during an experiment designed to investigate jaw, lip, laryngeal, and velar kinematics for normal and dysphonic speakers. The waveforms correspond to a single utterance of the vocal task /sma/ by a normal speaker and include, from top to bottom, the speech acoustic signal, the high-pass filtered electroglottographic (EGG) waveform,[7] the low-pass filtered EGG waveform, jaw and velar kinematic waveforms obtained from accelerometer transducers, and orbicularis oris and trapezius myoelectric waveforms obtained from bipolar surface electrodes. Additional waveforms (upper and lower lip movement and additional muscle activity) were obtained but not included in Fig 4 for the purpose of brevity.

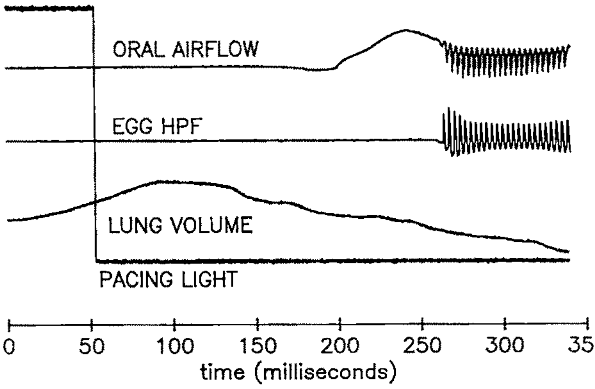

Fig 5. Composite graph of oral airflow, high-pass filtered electroglottographic (EGG HPF), total lung volume, and pacing light waveforms from which quantitative measures may be derived for one utterance of *hat*.

The analog-to-digital conversion process permits variable sampling rates across channels to efficiently accommodate slow- and fast-varying waveforms. For example, the speech acoustic waveform may be sampled at a rate of 20 kilosamples per second (ksps), the myoelectric signals at 5 ksps, and the jaw and velar kinematic signals at 0.25 ksps. Recorded events may be of any duration. The acquisition work station accommodates up to 12 waveforms from the signal interface. While 12 channels is satisfactory for many experimental studies, the system can be configured to include any number of additional channels by simple hardware and software modifications.

Because experimental data have been coded and organized by subject, session, task, and token, comprehensive analysis is accomplished by computer-automated processes that perform specific time- and frequency-domain calculations on the data base. Digital signal analyses such as spectral content, power content, temporal measures, reaction-time measures, and perturbation measures are organized and accomplished much more efficiently and effectively by computer than by hand for multiple measures in large volume. Answers to questions such as "What is the average voice onset time[8] (VOT) indicated by aerodynamic and glottal activity waveforms for utterances of the linguistic task /kuh/ by normal female speakers between the ages of 25 and 40 responding to pacing light signals of greater than 250 milliseconds' duration and, further, what is the average lung volume change in milliliters during the VOT interval?" are obtained from a computer-automated search of the data base.

For additional verification, quantitative results may be accompanied by automatically prepared

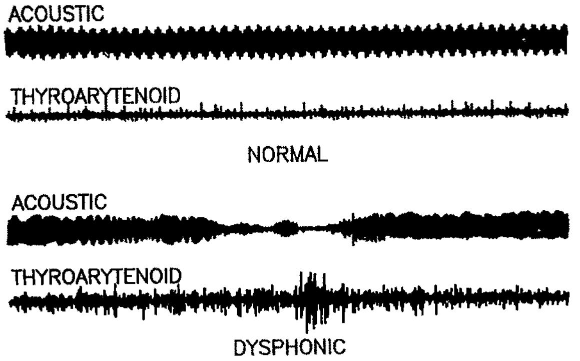

Fig 6. Qualitative acoustic and myoelectric comparisons for normal and dysphonic subjects in data base that are located, organized, and displayed by computer-automated processes.

graphic results that display time- and/or frequency-domain graphs indicating the specified measures. Figure 5 is a graph of composite waveforms (time-edited during the interval of interest) that is readily obtained with the computer-aided analysis system. Included in Fig 5 are the pacing light signal (refer to Figs 1 and 2), the EGG high-pass filtered waveform, the oral airflow waveform (obtained from a calibrated airflow plethysmograph[9]), and the total lung volume waveform (obtained from a calibrated respiration plethysmograph[10]) recorded during an utterance of the linguistic task *hat*. The graph demonstrates the versatility of the system to aid in the investigation of related physiologic events and to systematically extract quantitative measures. For example, signals in Fig 5 permit comparisons of changes in lung volume and peak volume velocity during the aspirated /h/, the interval between peak oral airflow and onset of vocal fold vibration for the following vowel as reflected in the EGG signal, and various reaction-time response measures obtained with the aid of the pacing light landmark. Accompanying the waveforms appearing in Fig 5 in the data base are time-synchronous EGG low-pass filtered, nasal airflow, rib cage volume, abdomen volume, and speech acoustic waveforms acquired during an experimental session designed to investigate airflow, glottal, and respiration dynamics.

Figure 6 illustrates speech acoustic and thyroarytenoid myoelectric waveforms for a normal speaker (upper pair) and a dysphonic speaker (lower pair) attempting to sustain the vowel /i/ at comfortable loudness and comfortable pitch. At date of testing, the normal subject was a 34-year-old man with no history of speech or language disorders. The dysphonic subject was a 44-year-old man with a clinical diagnosis of adductor spasmodic dysphonia.[11] Myoelectric signals were obtained with hooked-wire bipolar electrodes inserted percutaneously. For this example, the myoelectric signals were low-pass filtered at 700 Hz before digitization. The lower waveforms clearly indicate the spasmodic burst of the thyroarytenoid muscle during portions of the speech task and corresponding deterioration of the acoustic signal. Accompanying these waveforms in the data base are additional time-synchronous electromyographic waveforms obtained for a variety of tasks during an experimental session designed to investigate multiple myoelectric activity of the speech motor system.

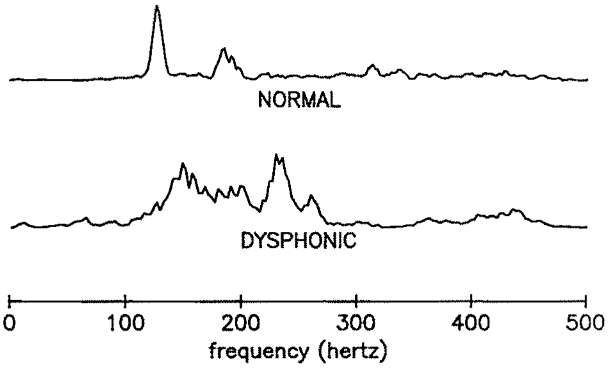

Fig 7. Quantitative spectral comparisons of normal and dysphonic myoelectric waveforms in Fig 6.

Figure 7 portrays spectral comparisons of the myoelectric waveforms presented in Fig 6 for the normal and the dysphonic speaker. The results in Fig 7 are obtained by squaring and normalizing discrete-Fourier transforms[12] from 1-second, artifact-free intervals of the thyroarytenoid myoelectric waveforms appearing in Fig 6. These spectral measures quantify power versus frequency content of the myoelectric signals[13] and illustrate the scattering of speech production activity across a much broader frequency range for the dysphonic speaker compared to the normal. For this example, the spectral graphs indicate the inefficiency of the spasmodic speech motor system in attempting to sustain the vowel /i/ at a steady pitch.

The time- and frequency-domain illustrations appearing in Figs 4-7 demonstrate some of the qualitative and quantitative results that are readily available from the computer work station by virtue of the described systems architecture. Further, they demonstrate the ability of this architecture to provide systematic organization of the data throughout the acquisition and processing stages so that valuable quantitative results may be obtained by powerful computer-aided processes.

Analysis of experimental data thus proceeds largely by comprehensive computer software programs designed to calculate composite measures for patient subjects for comparison with normal subject measures to better understand normal and disordered speech motor control. Results of these computer-automated procedures that quantify dynamic myoelectric and kinematic activity of the vocal motor system for spasmodic dysphonia patients will be the subject of later papers.

DISCUSSION

Speech production is a complex, multidimensional activity requiring coordinated control of many physiologic mechanisms: the abdomen, thorax, and lungs to provide dynamic airflow; the larynx as the sound source; a multitude of supralaryngeal articulators including the lips and tongue; and the oral and nasal cavities to further resonate and modify the acoustic signal.

Because of the complex nature of the speech motor system and of the speech acoustic signal itself, many researchers agree that experiments should be carefully designed to 1) be sensitive to the problems inherent in human testing; 2) contain a variety of multidimensional tasks — including vegetative, linguistic, and paralinguistic tasks — that exploit physiologic activity in one component of the speech motor system as well as concerted activity among multiple components; 3) include multiple tokens of these tasks to minimize effects of intratask variability, reduce artifacts, and increase data integrity; 4) provide for comparisons of many simultaneous measures within and across subjects; 5) compare quantitative measures obtained from many normal subjects to those derived from many patient subjects; and 6) provide a high level of reproducibility.[1,4,14]

At present, these dictates are only partially fulfilled. The ability of the laryngologist and speech scientist to study the coordinated activity of multiple physiologic mechanisms has historically been limited to only a few simultaneous signals and relatively few tasks and tokens. This limitation is due partly to the inherent difficulty of making direct or indirect measures of the involved physiology and partly to the enormous task of managing the acquisition and analysis of a large volume of multiple signals, sessions, subjects, tasks, and tokens in a convenient and time-efficient manner. This paper has presented a computer-managed systems architecture that advances the capability to accomplish the stated goals that are further discussed below.

Human Factors. The experimental acquisition session should be highly considerate of the subject, thereby minimizing the emotional and physical stress that can reduce performance. Therefore, it is imperative that the instrumentation and acquisition system be time-efficient and reliable. For patient subjects who participate in highly invasive sessions (perhaps nine percutaneous or endolaryngeal needle-inserted wire electrodes together with fiberoptic nasolaryngeal endoscopy), the acquisition system must reliably capture an enormous amount of data without interference to the subject, introduction of artifacts, loss of valuable subject activity, or loss of time. With reliable modern computers to organize the acquisition session (eg, interpretation of the task protocol, control of acquisition and recording instruments connected to the interface bus, and pacing light control), maximum attention can be directed to the subject. The session proceeds systematically, one token succeeding another, while the task of data collecting and coding is accomplished by computer control.

Tasks and Tokens. Experiments to comprehensively study the speech motor system usually contain a variety of tasks, ranging from complex to simple (in terms of temporal constraints and/or motor organization), and ranging from vegetative nonvocal to cognitive-linguistic.[14] The computer system accommodates these rich varieties of tasks as a matter of course. Experiments organized with this systems architecture may readily contain 100 tasks or more and prompt a sufficient number of tokens for each task. Furthermore, some experimental studies include reaction-time and rate-control tasks[5] that require special pacing light signals that prompt the subject's response to a visual stimulus. These time-sensitive tasks are likewise managed by the computer system and appropriately coded.

Quantitative Measures. A computer-managed systems architecture is essential because of the huge volume of data that are acquired from many subjects attending multiple sessions, each of which involve a large number of tasks and tokens. By virtue of coding the acquired data by subject, session, task, and token, procedures that access the data base are automated by computer programs. Examples that illustrate the advantages of this systems architecture in facilitating obtaining quantitative measures from the data base were discussed in the Results section of this paper.

Reproducibility. When measures derived from one experimental session are compared to measures derived from another session, it is imperative that the experiments be conducted under identical procedures and conditions. For example, measurement of cricothyroid myoelectric activity from a normal subject performing the nonspeech task the Valsalva maneuver should be acquired under conditions identical for the patient subjects as well as all other normal subjects, including instrumentation, calibration of reference, prompting of subject, recording technique, etc. A computer-assisted acquisition system maximizes reproducibility by organizing and conducting a systematic session. Valsalva tasks occur as one of a series of many start-stop recording sequences during the acquisition session and are presented identically for each successive session and subject. Reproducibility is an inherent advantage of a computer-managed acquisition system.

Flexible Data Base. Because of the enormous challenge of dealing with multiple time-synchronous signals in large volume, such data have historically been organized, stored, and analyzed in ways convenient only to the original goals of the initial study. Data preparation and analysis procedures were performed according to the efficient use of time, personnel, and mass storage resources that satisfied the original research intent. For example, studies to examine VOT or reaction-time intervals stored, organized, and analyzed the data specific to the goal at hand. Future analysis of the data often required repeating many (if not all) of the procedures to structure the raw data under a new guise, including sequential access of the original data files on the tape media, redigitization, editing new time-windows for pertinent tasks and signals, etc.

Once data are organized according to the systems architecture described here, further investigations of the data base may be undertaken without the need to reaccess and reorganize the original signal data. Intermediate and final results of any analysis procedure may be uniquely coded according to the rules outlined in Table 2 (in particular, new Edit numbers and File code numbers) and included in the data base if desired. Valuable investigator time is salvaged from mundane repetitive tasks that are error-prone and thus is available to concentrate on tasks that are the focus of investigations. The relatively new optical storage devices, coupled with the convenience of the personal computer, have made compact mass storage economically affordable to researchers desiring local access to their data base.

These goals are accomplished with modern microcomputer systems properly configured and programmed to fulfill the stated objectives. This paper has presented such a system implemented with a relatively inexpensive but powerful desktop computer. The computer-aided data acquisition and analysis system presented here should prove a useful adjunct to laboratories conducting comprehensive investigations of speech. The system provides a user-friendly menu-driven interface and is readily configurable to other, similar tasks in health science.

This computer-aided system may be configured with essentially any IBM AT–type desktop computer. Desktop computers have many advantages over their mainframe counterparts, including being much less expensive to purchase, operate, and maintain; more reliable; easier to program and use; easily configurable to a variety of tasks; providing a standardized interface to instruments; task-dedicated; readily transportable; and providing a standardized architecture accepting a wealth of available software.

Personal computers are used throughout the health science industry to perform a multitude of tasks for research and clinical professionals. Their use to accomplish the complex task of entirely organizing the acquisition and analysis of enormous volumes of experimental data that, in the end, rival the capabilities of mainframe computer systems has not been reported. In the past, few research groups have dedicated the personnel and monetary resources required to develop such a system. Therefore, most speech research laboratories have been without the dedicated computing essentials to manage the acquisition and analysis tasks described here and hence to efficiently conduct comprehensive investigations of this magnitude.

Hardware components of the desktop computer–based acquisition and analysis work station, as listed in Table 1, cost approximately $60,000. Researchers and clinicians without the need for a multichannel tape recording device (thus recording multiple channel data directly to computer disk media) can configure a system for $35,000. Further omissions of unneeded components decrease costs accordingly.

CONCLUSIONS

A systems architecture has been described that provides a powerful mechanism for the acquisition, organization, and analysis of multiple, time-synchronous signals in large volume. This systems architecture was developed by our research group as a birthchild of necessity — to advance our investigations of the speech motor system to the next explorative level and thereby develop a more complete understanding of speech production physiology and central nervous system organization.

It has been the goal of this research group to demonstrate the viability of this systems architecture as it is implemented in the format of an inexpensive personal computer and yet provide a powerful and highly efficient tool comparable to systems costing much more. This system should provide a cost-efficient research and clinical device to *any* application requiring the management of multiple signals in large volume. It should permit many more researchers to participate in comprehensive investigations of speech production and speech pathology.

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Ann Otol Rhinol Laryngol 99:1990

FACIAL NERVE MONITORING IN OTOLOGIC SURGERY: CLINICAL INDICATIONS AND INTRAOPERATIVE TECHNIQUE

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While identification of the intratemporal portion of the facial nerve is mandatory in most otologic surgical procedures, inadvertent instrumentation, traction, or thermal injury may still result from inaccurate delineation, purposeful avoidance, or false protection of this critical structure. Improved functional preservation of the facial nerve has been achieved in acoustic neuroma surgery through the monitoring of evoked facial electromyographic activity. This technique may also be used during otologic procedures in which facial nerve manipulation is anticipated in the management of recurrent cholesteatoma, temporal bone trauma, congenital deformity, or purposeful access for cochlear implantation. Potential indications for using facial nerve monitoring in contemporary otologic surgery are detailed through illustrative case presentations, and necessary instrumentation and techniques are briefly reviewed. Intraoperative monitoring can assist the surgeon in isolating the facial nerve when chronic inflammation, traumatic injury, or anomalous development has resulted in distortion or absence of microanatomic landmarks.

KEY WORDS — facial nerve monitoring, otologic surgery.

INTRODUCTION

"Knowledge of the precise relationship of the facial nerve to other landmarks in the temporal bone is the basic requirement for safe, effective temporal bone surgery."[1]

The facial nerve is one of the most crucial landmarks used in temporal bone surgery. Respect for the normal and potentially aberrant intratemporal course of this structure is and will remain a mandatory prerequisite to successful otologic surgery. Intraoperative monitoring of evoked facial electromyographic (EMG) activity, used commonly in neurotologic surgery,[2] may supplement one's knowledge of temporal bone anatomy during otologic procedures in an effort to improve functional preservation of the facial nerve.

METHOD

During the period between July 5, 1988, and January 5, 1990, a total of 129 major otologic surgical procedures were performed at Loyola University Medical Center by the same surgeon (J.P.L.). All procedures were performed under general anesthesia, required a minimum overnight in-hospital stay, and involved at least a mastoidectomy or craniotomy. Sixteen of these procedures were performed with the assistance of intraoperative facial nerve monitoring.

The criteria for using intraoperative monitoring of the facial nerve were purely subjective and were determined by a combination of preoperative clinical and radiographic findings. Facial twitching, resolved facial paresis, or an exposed facial nerve documented by prior operative reports were clinical indications for the use of intraoperative monitoring, while significant fallopian canal distortion as shown on computed tomography (CT) was a radiographic indication for using monitoring.

Intraoperative facial nerve monitoring was used in 16 of the 129 cases. Of the 9 patients with chronic otitis media and cholesteatoma, 5 presented with intracranial complications, 2 demonstrated facial twitching, and all had fallopian canal erosion noted on CT evaluation. All 4 patients with congenital aural atresia had undergone at least one prior surgical procedure, and 1 patient presented with an associated congenital hemifacial microsomia. Two patients underwent otologic procedures for the repair of cerebrospinal fluid (CSF) fistulae and hearing restoration following resolution of delayed facial paralysis, and 1 patient required an extensive cochlear "drill-out" during an attempted cochlear implant procedure.

FACIAL NERVE MONITORING

The guidelines for monitoring facial EMG activity during surgical dissection have been previously outlined.[3] All monitoring was performed with the Xomed Nerve Integrity Monitor (NIM-2), which provides audible output in real time as well as visual output on an oscilloscope display. Open communication between the surgeon and the designated electrophysiologist seated in front of the NIM-2 unit allows interpretation of all evoked responses throughout the procedure.

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Presented at the meeting of the American Otological Society, Inc, Palm Beach, Florida, April 28-29, 1990.

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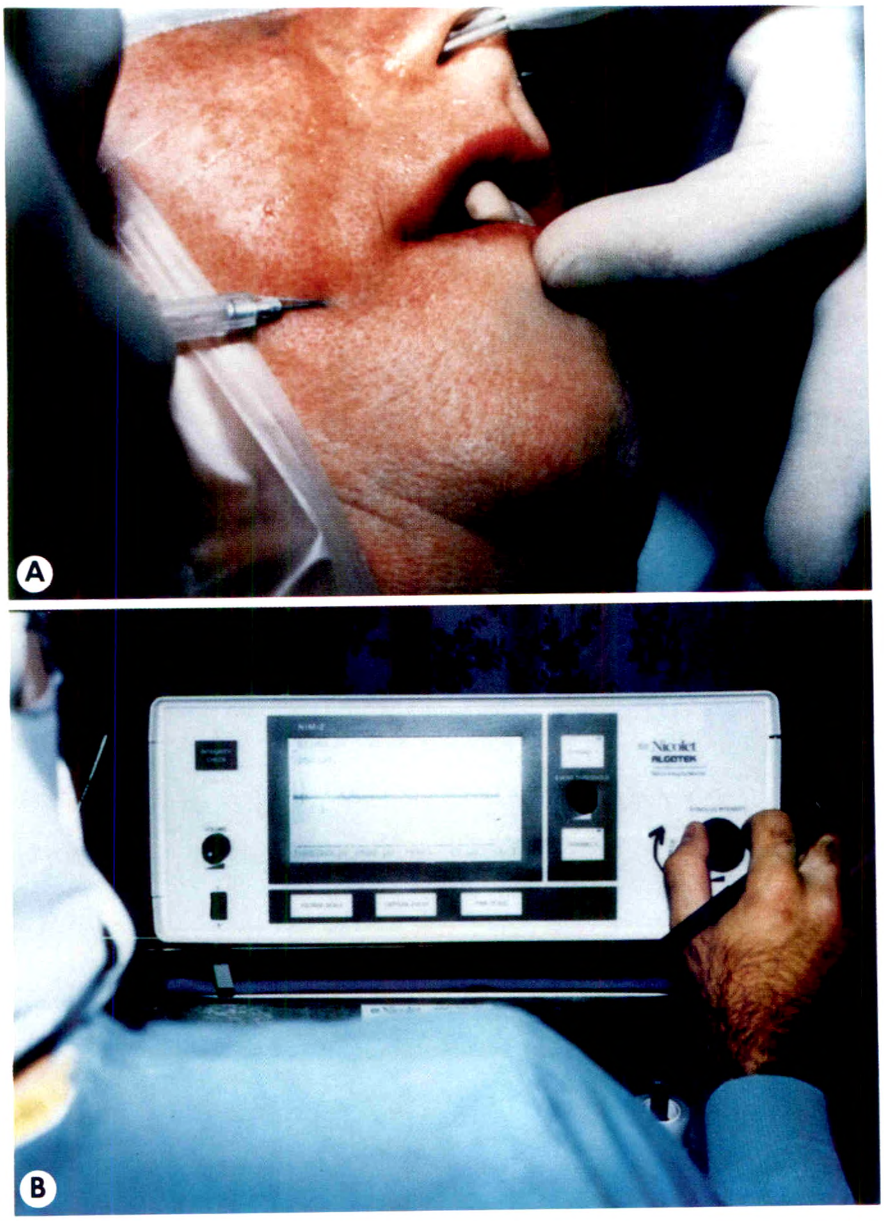

Fig 1. (Case 1) A) Bipolar hook wire electrode placement into orbicularis oris muscle. B) "Tap test" response displayed as spike on oscilloscope. See text for detailed description.

After the induction and maintenance of general anesthesia without muscle relaxant administration, bipolar hook wire electrodes are placed in the ipsilateral orbicularis oculi and orbicularis oris muscles.[4] Electrical impedance valves of 10 to 25 kΩ are verified by use of the integrity check visual screen, and a complete systems check is performed by gently tapping the electrode placement sites (Fig 1). This "tap test" will provide audible "pops" as well as visual "spikes" on the oscilloscope that directly correlate with each mechanical stimulation. Baseline EMG activity is normally between 11 and 19 μV.

ELECTRICAL STIMULATION

A Xomed-manufactured, Prass monopolar flush-tipped cathode stimulator is used, at the surgeon's discretion, to help differentiate the facial nerve from surrounding scar or granulation tissue or to help map the exact course of the nerve when it is abnormal as a result of trauma or congenital deformation. Stimulus intensity varied between 0.05 and 0.2 mA depending upon the degree of exposure of the facial nerve at the site of stimulation.

TECHNIQUE AND INTERPRETATION

The system is placed in the full "on" position during bone drilling and microdissection and is muted only during electrocautery usage.[5] Audible responses to evoked EMG activity have been classified as brief (bursts or pops) or sustained (trains).[3] Momentary stimulation of the facial nerve with a diamond bit or blunt dissecting instrument results in burst responses, whereas thermal injury, neural traction, or prolonged impingement on the nerve causes train activity. Visual and audible responses

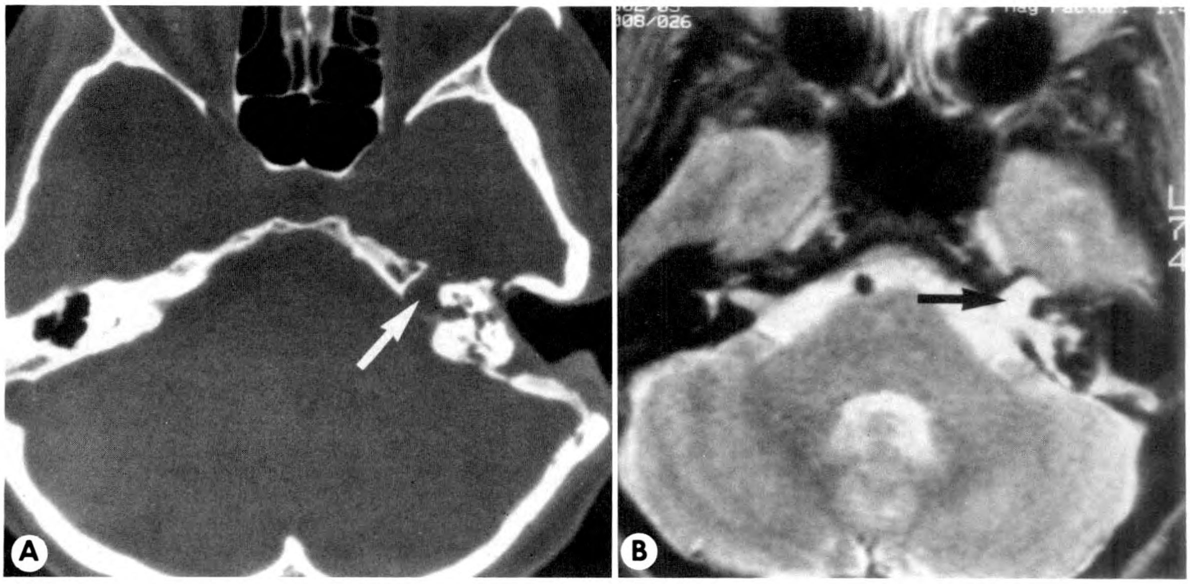

Fig 2. (Case 1) Petrous apex cholesteatoma (arrows) seen on A) axial computed tomography and B) magnetic resonance imaging.

are interpreted individually by both the operating surgeon and the monitoring personnel throughout the surgical procedure.

None of the 16 patients developed persistent facial paralysis, although 1 patient sustained a partial weakness that resolved within 2 months of the operation. The following case presentations will illustrate the usefulness of facial nerve monitoring during otologic procedures.

CASE REPORTS

CHRONIC OTITIS MEDIA

Case 1. A 65-year-old woman presented with persistent otorrhea 9 months following a radical mastoidectomy for an extensive, recurrent cholesteatoma. She also complained of occasional stabbing-like left temporal headaches and the recent onset of ipsilateral facial twitching.

Weeping granulation tissue was present over the tegmen mastoideum, and entrapped epithelium was visible in the sinodural angle. Left midfacial and periorbital twitching that was apparent at rest became more pronounced following voluntary blinking.

A severe to profound left sensorineural hearing loss with poor speech discrimination was noted in the left ear, and CT analysis demonstrated petrous apex erosion by a nonenhancing lesion that was isodense with the brain. Magnetic resonance imaging showed this soft tissue mass to be more prominent on T2 than on T1 views (Fig 2).

Radical marsupialization of this petrous apex cholesteatoma was performed through a translabyrinthine-transcochlear approach with skeletonization of the facial nerve, jugular bulb, and petrous carotid artery (Fig 3). Initial elevation of the mastoid cavity soft tissue in the area of the facial ridge resulted in brief evoked responses ("pops") due to dehiscence of the vertical segment of the facial nerve. Sharp dissection under high microscopic power was performed in order to safely isolate the facial nerve in this region. Brief "pops" were also noted during skeletonization in the labyrinthine and perigeniculate regions, and a 15-second sustained evoked response ("train") was noted during transection and mobilization of the greater petrosal nerve.

A partial peripheral facial weakness was noted in the midface and lower lip regions in the immediate postoperative period, but good recovery was noted by the second postoperative month (Fig 4).

Comment. Facial nerve dehiscence may occur in any patient with chronic otitis media.[6] However, extensive complete exposure of the nerve in the vertical segment is fairly uncommon. Intraoperative monitoring was useful during dissection of scar tissue away from the facial nerve and assisted in the relatively safe, gentle, yet expeditious decompression and mobilization of the nerve.

CONGENITAL AURAL ATRESIA

Case 2. A 24-year-old man with unilateral congenital aural atresia and hemifacial microsomia presented with 3 months of right-sided otorrhea and jaw pain 4 years following a canalplasty with skin graft repair.

The right external auditory canal was obstructed by a bony stenosis posteriorly and the skin-grafted mandibular condyle anteriorly. Squamous debris could barely be aspirated through the slitlike meatus — only with jaw opening. Although this patient demonstrated no frontal or periorbital facial

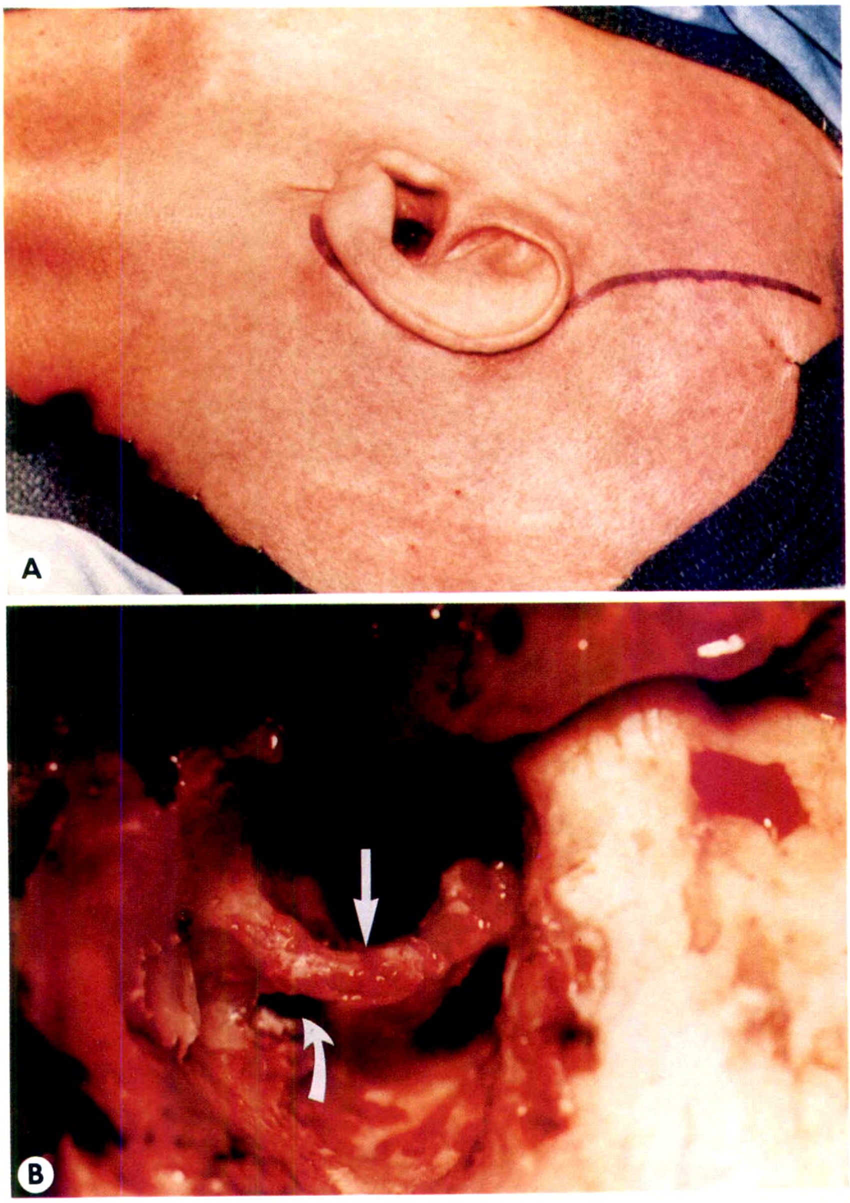

Fig 3. (Case 1) Translabyrinthine-transcochlear approach to petrous apex cholesteatoma. A) Incision marks. B) Note skeletonized facial nerve (straight arrow) and exposed jugular bulb (curved arrow).

movement, animation was present in the midface, perioral, and cervical neck regions (Fig 5).

An expected conductive hearing loss was documented in the involved ear, and a preoperative CT scan confirmed the presence of a bony external meatal stenosis as well as an entrapped soft tissue mass filling the narrowed canal (Fig 6).

A revision meatoplasty was performed with evacuation of an external canal cholesteatoma. Facial nerve activity was noted during drill dissection medial to the mandibular condyle and lateral to the bony annulus. A bifid facial nerve was identified in this region that coursed inferior to a malformed stapes within the middle ear.

Preoperative facial function was preserved, and a dry, patent meatus is evident 16 months following the operation.

Comment. Anatomic variations of the facial nerve may occur in conjunction with congenital ear anomalies.[7] Definitive identification by microscopic visualization alone may be time-consuming and painstakingly difficult in previously operated, scarred tissue with surrounding cholesteatoma. Careful bone dissection with a diamond drill bit under microscopic control was supplemented by facial nerve monitoring in the identification and preservation of the anomalous facial nerve in this case. Definitive mapping of the nerve's path was possible through judicious use of a monopolar stimulating probe.

TEMPORAL BONE TRAUMA

Case 3. A 35-year-old woman presented with left-sided hearing loss and recurrent sporadic CSF otorrhea 4 months after sustaining a severe temporoparietal skull fracture in a motor vehicle accident. A complete, ipsilateral, peripheral facial paralysis

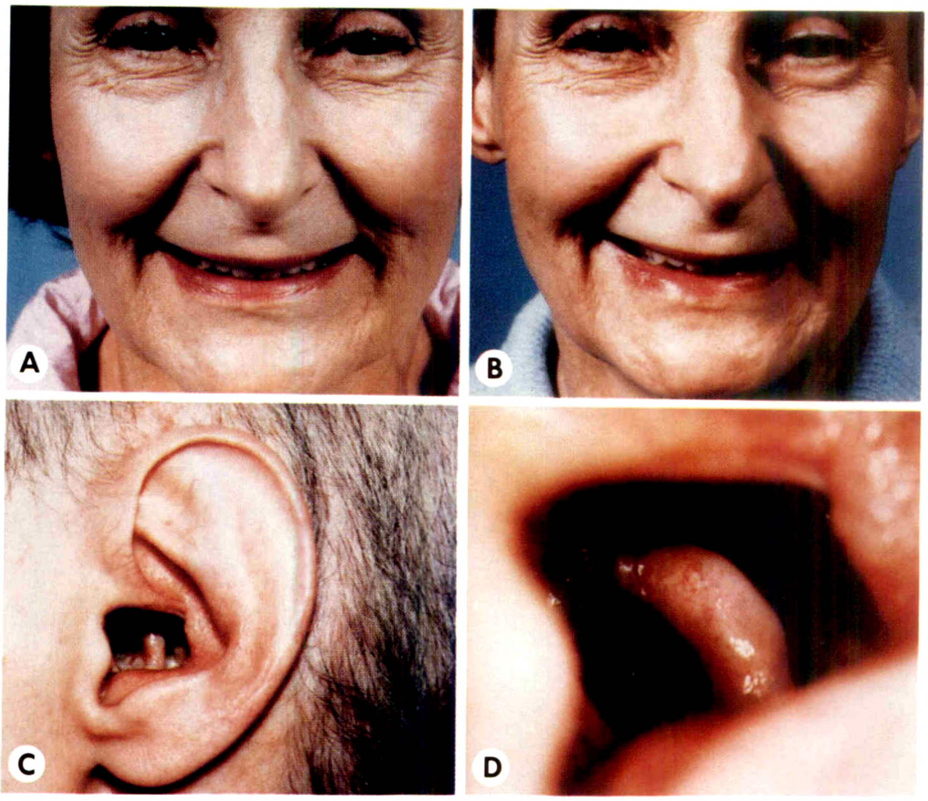

Fig 4. (Case 1) A) Preoperative and B) 10-day postoperative facial function in patient with petrous apex cholesteatoma. Note C) epithelialized mastoid cavity and D) facial nerve 5 weeks following radical marsupialization of cholesteatoma.

had resolved at the time of presentation.

The left middle ear was filled with clear fluid, and an atrophic, healed perforation of the anterior pars tensa was coated with friable granulation tissue.

Audiometric testing confirmed the presence of a mixed hearing loss in the right ear, and CT demonstrated a temporal bone fracture through the tegmen tympani, mastoid, and external auditory canal (Fig 7). Results of the analysis of the middle ear aspirate via tympanocentesis were compatible with CSF.

A transmastoid-transcanal approach was used to repair a comminuted tegmen tympani defect and to reconstruct the ossicular chain. Upon elevation of the dura over the middle cranial fossa, sustained facial EMG activity was observed. Comminuted bone fragments had compressed the facial nerve at the geniculate ganglion and were further impinging on the nerve following dural elevation in this region. The bony spicules were carefully removed, and the dural defect was repaired with a fasciomuscular graft. The posterosuperiorly displaced incus was transposed between the malleus and the stapes, and a fascia tympanoplasty was performed.

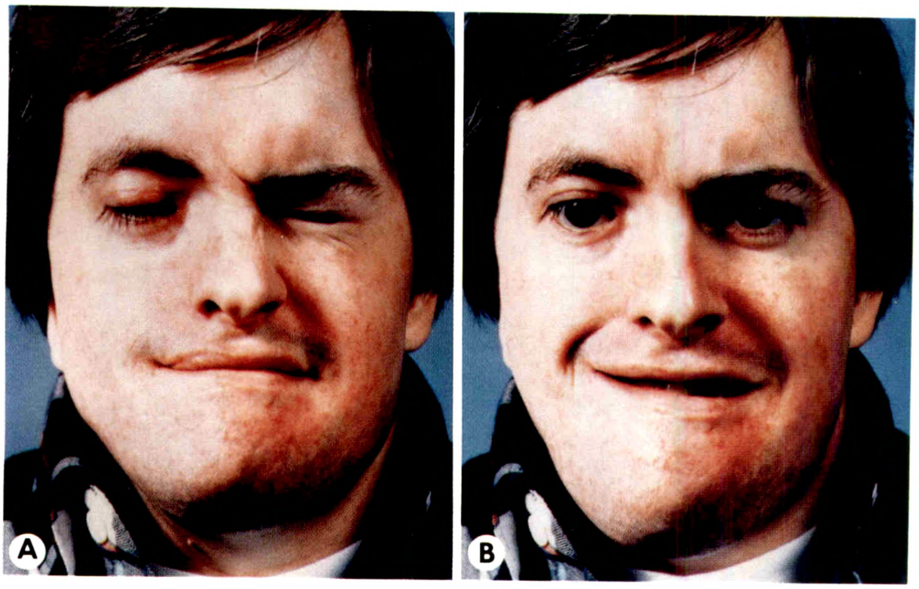

Fig 5. (Case 2) Patient with right congenital aural atresia and hemifacial microsomia. Note A) partial eye closure and B) midface animation.

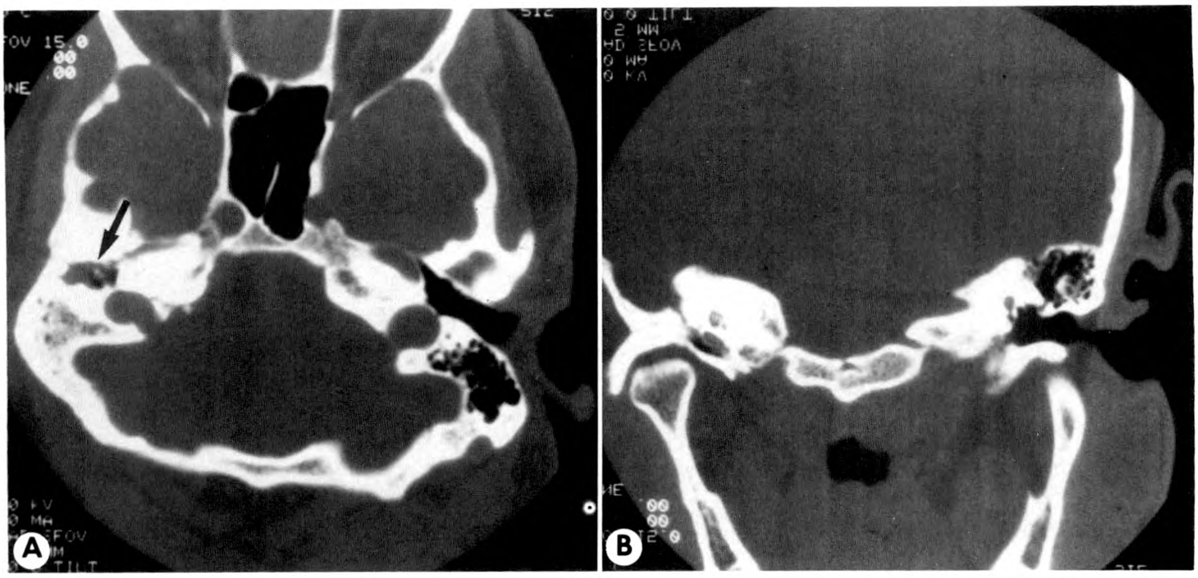

Fig 6. (Case 2) Computed tomograms showing right congenital aural atresia with external ear canal cholesteatoma (arrow). A) Axial. B) Coronal.

Preoperative facial function was preserved, the CSF leak ceased, and partial closure of the air-bone gap was achieved.

Comment. Facial nerve injury following blunt head trauma usually occurs in the perigeniculate region.[8] In this patient with recovered facial function, surgical exploration for hearing restoration and CSF leakage may have resulted in additional facial nerve injury. Dissection and elevation of the middle fossa dura caused tethering of the nerve along comminuted bony fragments that was immediately identified by sustained, evoked EMG activity. Dural elevation was stopped until the bone fragments were dissected away from the nerve, and safe completion of the surgical procedure was performed with preservation of facial nerve function.

COCHLEAR IMPLANT SURGERY

Case 4. A 32-year-old woman presented with bilateral profound sensorineural hearing loss resulting from meningitis at age 12. Findings on clinical evaluation were unremarkable, with the exception of her above-mentioned hearing loss, and high-resolution CT scanning demonstrated abnormal fibrous obstruction of the cochleae compatible with her history of meningitis (Fig 8).

A right cochlear implant was attempted through the usual facial recess approach; however, thick

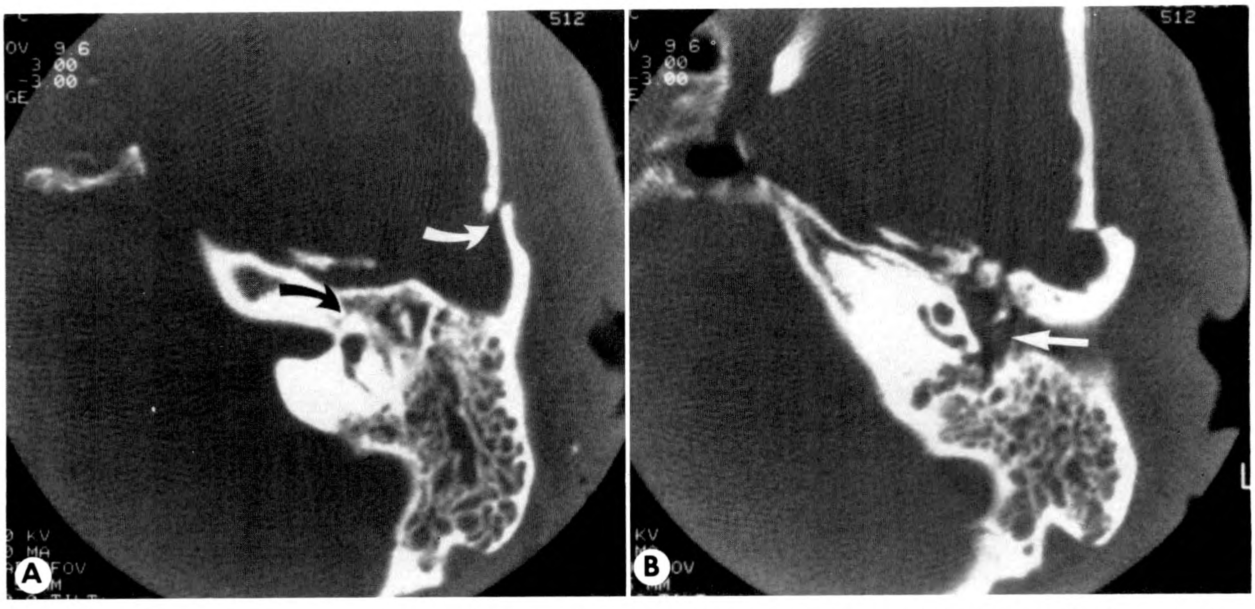

Fig 7. (Case 3) Computed tomograms showing left temporal bone fracture sustained in motor vehicle accident. A) Note depressed parietal (white arrow) and perigeniculate (black arrow) fractures. B) Cerebrospinal fluid fills middle ear space (arrow).

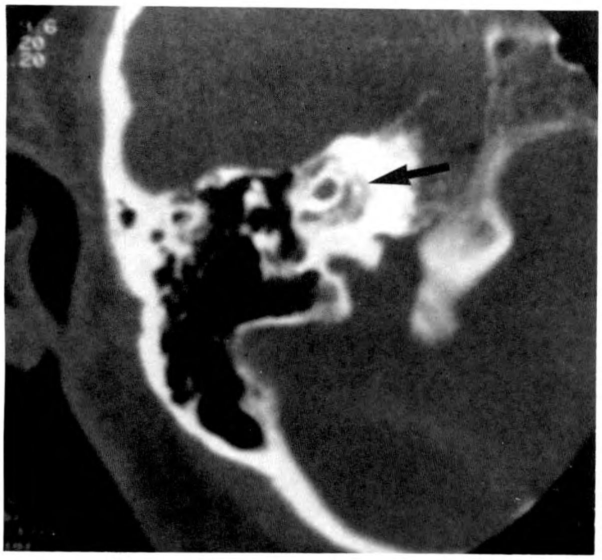

Fig 8. (Case 4) Computed tomogram showing fibro-osseous cochlear obstruction (arrow) in patient with meningitic sensorineural deafness.

yellow fibro-osseus connective tissue was noted to have replaced the entire scala tympani. During this extended "drill-out" of the basal cochlear turn and superior dissection along the posterior carotid wall, brief bursts of facial nerve activity were elicited, as the shaft of the drill bit had exposed the anterior inferior aspect of the vertical segment of the facial nerve. Drill activity was discontinued, the perineurium was cooled with saline irrigation, and bone wax was applied to the exposed neural segment.

Despite additional drill curettage in search of a suitable lumen for implantation, it was decided not to attempt a partial implantation or "lay-in" procedure, on the basis of the preoperative psychosocial evaluation of this patient.

Her postoperative course was uneventful, normal facial function was preserved, and the patient continues to communicate through sign language.

Comment. Facial nerve identification and skeletonization is mandatory if cochlear implantation is performed through the facial recess approach. Standard drill cochleotomy near the round window does not usually jeopardize the facial nerve. However, prolonged drilling in the anterior and superior directions in an effort to follow the basal cochlear turn may result in thermal injury. Exposure of the vertical facial nerve segment may occur if the drill or drill bit shaft is angled posteriorly and inadvertently fulcrumed on the facial nerve. Intraoperative monitoring of the facial nerve was helpful in alerting the surgeon to this event so that appropriate measures could be taken to protect the exposed nerve segment.

DISCUSSION

Iatrogenic injury to the facial nerve resulting in paralysis has been reported to occur in 0.6% to 3.6% of otologic surgical procedures.[9] Technical aspects of otologic surgery, such as proper drill-bit selection, adequate cool irrigation to prevent thermal nerve injury, and drilling parallel to the facial nerve are certainly helpful and necessary. But the single most important way to avoid injury to the facial nerve is to know the course of this structure as it relates to a variety of other landmarks within the temporal bone.[10]

Normal facial nerve anatomy may be distorted following temporal bone trauma or in cases of anomalous development.[11] The facial nerve may also suffer from prolonged irritation as in chronic otitis media with or without cholesteatoma impingement.[12] Finally, inadvertent injury to the facial nerve during an otologic procedure, despite proper identification, may result in postoperative facial paralysis.

Improved preservation of facial nerve function following a variety of skull base surgical procedures has been achieved, in part, through the use of intraoperative acoustic facial EMG monitoring.[13] We feel that in selected cases intraoperative facial nerve monitoring is also useful during otologic procedures.

Our subjective criteria for using facial nerve monitoring consist of a combination of clinical and radiographic findings that suggest a greater than normal risk of injury to the facial nerve if a surgical procedure is contemplated. For example, clinical indications might include any history of previous facial paralysis, any evidence of facial nerve irritation (twitching), or any suggestion of a previously exposed or injured facial nerve (prior operative reports). Computed tomographic scans in the axial and coronal projections can demonstrate facial nerve distortion due to trauma or infection, and are useful in determining cochlear patency prior to a cochlear implant operation. Patients with severe anatomic distortion or anomalous facial nerve paths may benefit from intraoperative monitoring, as will cochlear implant patients, who may require extensive "drill-out" procedures.

Only about 12% (16 of 129) of the major otologic surgical procedures in an 18-month period were performed with the aid of intraoperative facial nerve monitoring. Although none of these patients developed sustained postoperative facial weakness, it is not the purpose of this paper to state that facial paralysis can be avoided through only the use of evoked EMG activity monitoring. Nor are we stating that similar results would not have been achieved had monitoring not been employed. We do feel, however, that in specific cases in which the risk of facial paralysis seems higher than normal on the basis of clinical or radiographic analysis the use of intraoperative monitoring of evoked EMG activity can supplement the surgeon's knowledge of facial nerve anatomy in order to preserve facial nerve function during otologic procedures.

SUMMARY

Sixteen patients underwent major otologic surgical procedures while their facial nerve function was intraoperatively monitored via acoustic EMG techniques. Our method and indications for using intraoperative facial nerve monitoring were illustrated in the case presentations, and specific ways in which monitoring may prove helpful in otologic surgery were discussed.

ACKNOWLEDGMENT — The authors thank Jackie Burns for her critique and preparation of this manuscript.

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ENDOSCOPY OF THE COCHLEA DURING COCHLEAR IMPLANTATION

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We have previously demonstrated that multichannel cochlear implants may be effective in partially obstructed cochleas. In practice, however, it may be difficult to determine whether electrode insertion is feasible prior to attempting it. Initial trials with a flexible fiberoptic otologic endoscope on 10 cadaver temporal bones were previously reported. On the basis of these trials, endoscopy of the inferior segment of the cochlea during cochlear implantation seemed feasible. In the present study, the same endoscope was used on eight subjects undergoing cochlear implantation, six of whom had partially obstructed cochleas. Endoscopy was found to be helpful in visualizing obstructed segments, determining patency after the obstruction was removed, and identifying normal structures of the cochlea. Documentation with videotape and 35-mm photography constitutes the majority of this paper.

KEY WORDS — cochlea, cochlear implant, endoscopy.

Profound sensorineural hearing loss may be associated with obstruction of the fluid spaces of the cochlea more frequently than once recognized. This obstruction usually takes the form of new bone growth and has been reported in association with a variety of causes[1,2] in patients undergoing cochlear implantation: meningitis, autoimmune diseases, ototoxicity, otosclerosis, congenital disorders, Meniere's disease, malignant otitis externa, and trauma.

Although high-resolution computed tomography (HRCT) is usually helpful in identifying the presence and extent of cochlear osteoneogenesis, it may be misleading. False-normal HRCT findings have been reported in up to 46% of cases of surgically demonstrated cochlear obstruction.[1-4] Jackler et al[2] believe that the only assured way to determine cochlear patency is with an "exploratory cochleostomy." In a previous study we found that in 15 cases of partial bony obstruction of the inferior segment of the cochlear basal turn, complete insertion of long multichannel intracochlear electrodes was possible in 14 cases (93%). Functional results were equivalent to what might be expected in open cochleas.[1]

In practice, however, it may be difficult to determine whether full electrode insertion is feasible prior to attempting it. Descriptions of insertion techniques stress that insertion is relatively "blind" and that attempts at insertion must be discontinued when resistance is blindly felt.[5-7] Because of the cost of the devices currently available and the fact that once in contact with the patient such a device cannot be resterilized for reuse on another patient, endoscopy of the cochlea prior to attempted electrode insertion may hold potential advantages.

MATERIALS AND METHODS

A small-diameter flexible fiberoptic otologic endoscope has previously been described.[8] This device is 0.7 mm or 1.0 mm in diameter and contains 1,600 quartz fibers in a light guide cable. The effective length is 60 mm. It is designed with an otologic handpiece, is sterilizable with ethyl alcohol, and is immersible in glutaraldehyde. It is adapted for use

PATIENT DATA

Patient	*Cause of Deafness*	*Age at Onset of Deafness (y)*	*Age at Implantation (y)*	*High-Resolution Computed Tomography Findings**	*Operative Findings†*	*Insertion Length (No. of Rings)*
1	Congenital	0	7	C-0	Normal	32
2	Otosclerosis	50	56	C-2	Soft bone; 8 mm	32
3	Unknown	65	68	C-2	Hard bone; 8 mm	32
4	Rubella	5	34/43	N/A	Fibrous sheath; 8 mm	24
5	Congenital	0	18	C-0	Hard bone; 2 mm	23
6	Unknown	33	63	C-2	Soft bone; 6 mm	24
7	Otosclerosis	42	48	C-1	Soft bone; 4 mm	22
8	Meningitis	14	39	C-0	Normal	32

N/A — not applicable.

*Categories of obstruction seen radiographically as described in Balkany et al.[4]

†Bone subjectively categorized as hard or soft by surgeon at time of removal. Distance of obstruction measured from round window toward ascending turn.

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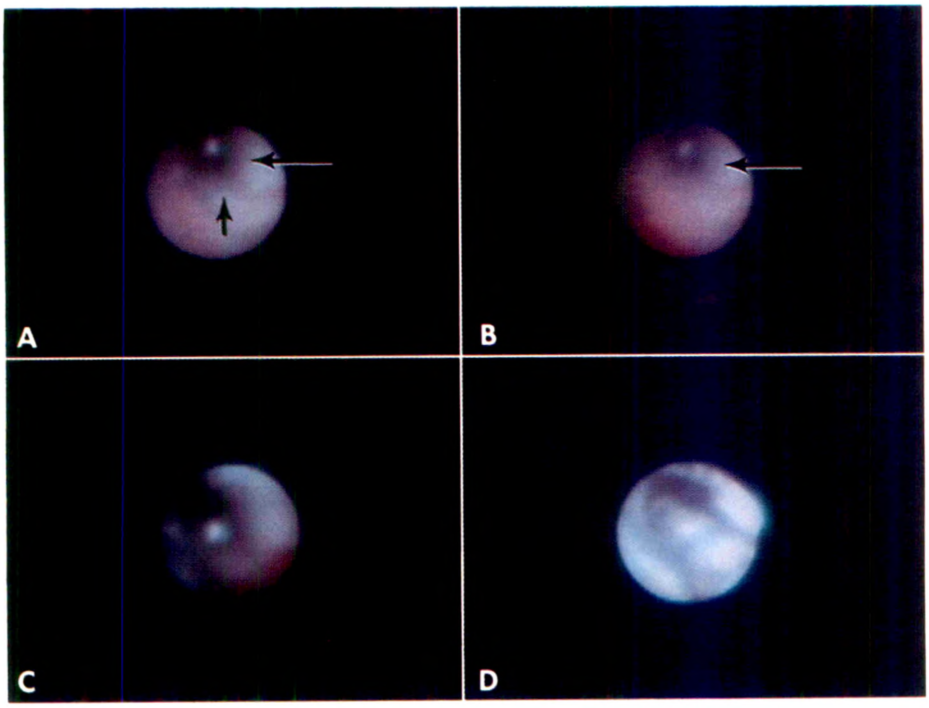

Fig 1. (Case 1) A) Patent scala tympani at 3-mm depth. Note smooth glistening appearance. Long arrow — basilar membrane, short arrow — spiral ligament. B) Scala tympani at 8 mm showing beginning of ascending turn. Arrow — basilar membrane. C) Electrode is seen to left in midportion of inferior segment. Basilar membrane is seen to right. D) Electrode is seen entering ascending turn.

with direct vision, a video camera, or a 35-mm camera. The field of vision is 55° with a depth of focus of 1 to 25 mm and a magnification of 60x. In a previous study on human temporal bones we demonstrated the relative safety, limitations, and potential efficacy of this device.[8]

In this study, endoscopy was performed on eight subjects undergoing cochlear implantation in accordance with the protocol approved by the Institutional Review Committee (functioning as the more commonly named Institutional Review Board and Human Subjects Committee). Ages ranged from 9 to 68 years. There were four males and four females. Of these eight, five had cochleas thought to have bony obstruction limited to the inferior segment of the basal turn and three had cochleas thought to be open on the basis of preoperative HRCT. The causes of deafness are listed in the Table.[4] All patients were implanted with Nucleus Mini-22 cochlear implants (Cochlear Corp, Englewood, Colo).

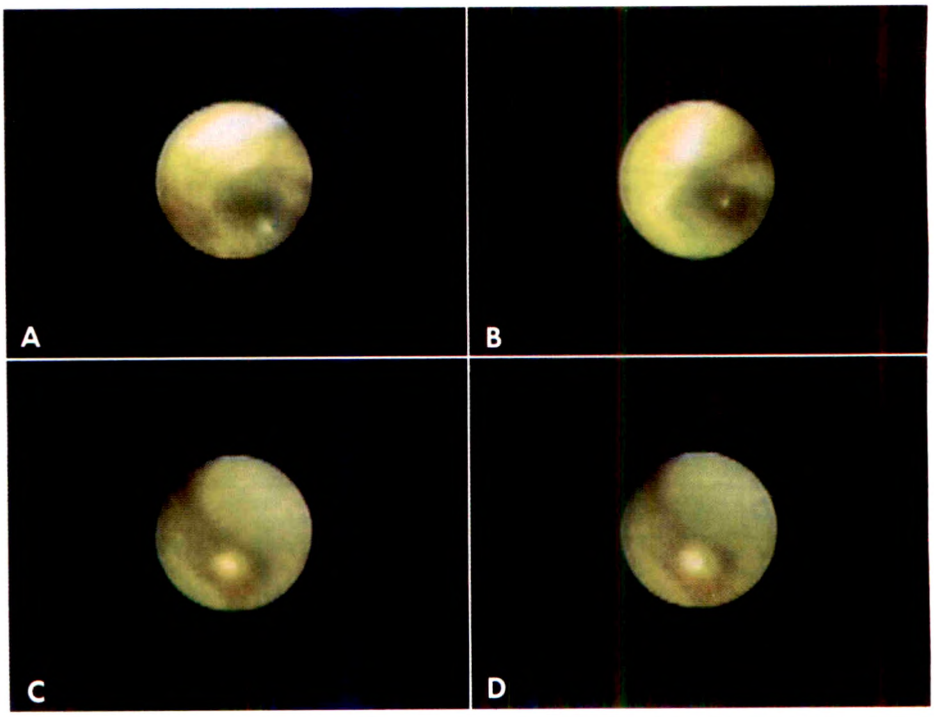

Fig 2. (Case 2) A) Irregular otospongiotic bone obstructing scala tympani at 4 mm. B) At 6 mm, scala appears patent. C,D) Further insertion demonstrates dead end at 8 mm.

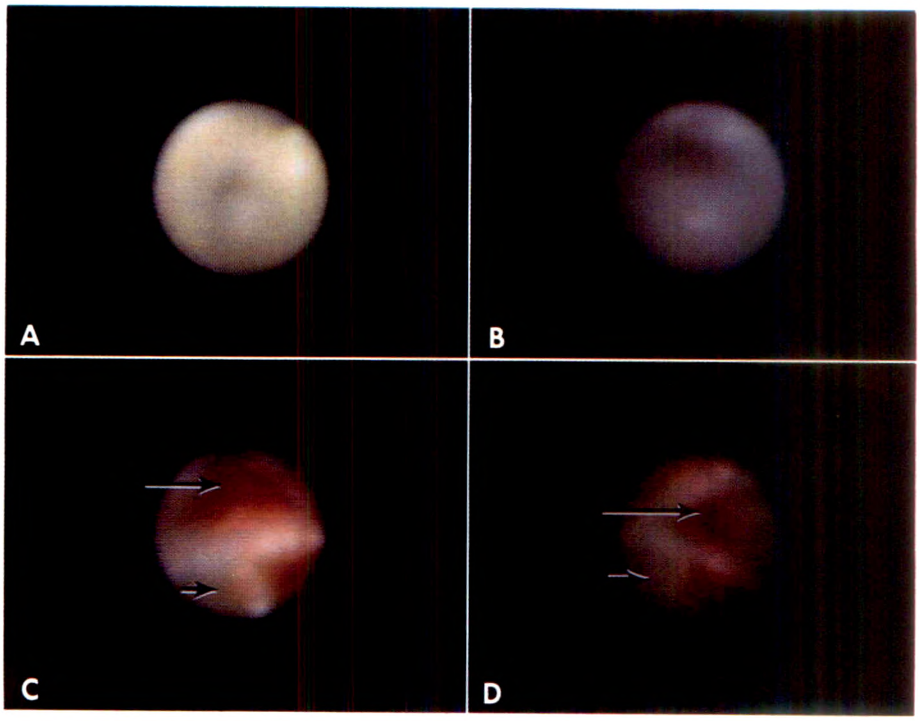

Fig 3. (Case 3) A) Hard bone obliteration of scala at 3 mm. Note smooth, regular appearance as contrasted with irregular bone of Fig 2. B) Perilymph is freed at 5 mm. C,D) At 7 mm, inferior segment has opened and both scala tympani (long arrow) and scala vestibuli (short arrow) can be seen divided by basilar membrane.

CASE REPORTS

Case 1. A congenitally deaf 7-year-old girl underwent a complete cochlear implant evaluation. Her preoperative HRCT findings were entirely normal. Her cochlea was normal in appearance at operation. Figure 1A,B demonstrates an open scala tympani with smooth, regular basilar membrane and spiral ligament well seen. Figure 1C,D demonstrates the 22-channel electrode in place in the inferior segment and traversing the ascending turn. This patient had a complete insertion of 32 rings and has not yet undergone initial tune-up.

Case 2. A 56-year-old woman with a long-term diagnosis of otosclerosis had undergone several attempts at stapedectomy elsewhere in the past. She had been profoundly deaf in both ears for approximately 6 years. She communicated primarily by lipreading and did not receive significant benefit from high-power binaural hearing aids. She underwent a complete cochlear implant evaluation and was scheduled for implantation. The HRCT demonstrated obliterative otosclerosis (spongiosis) with the

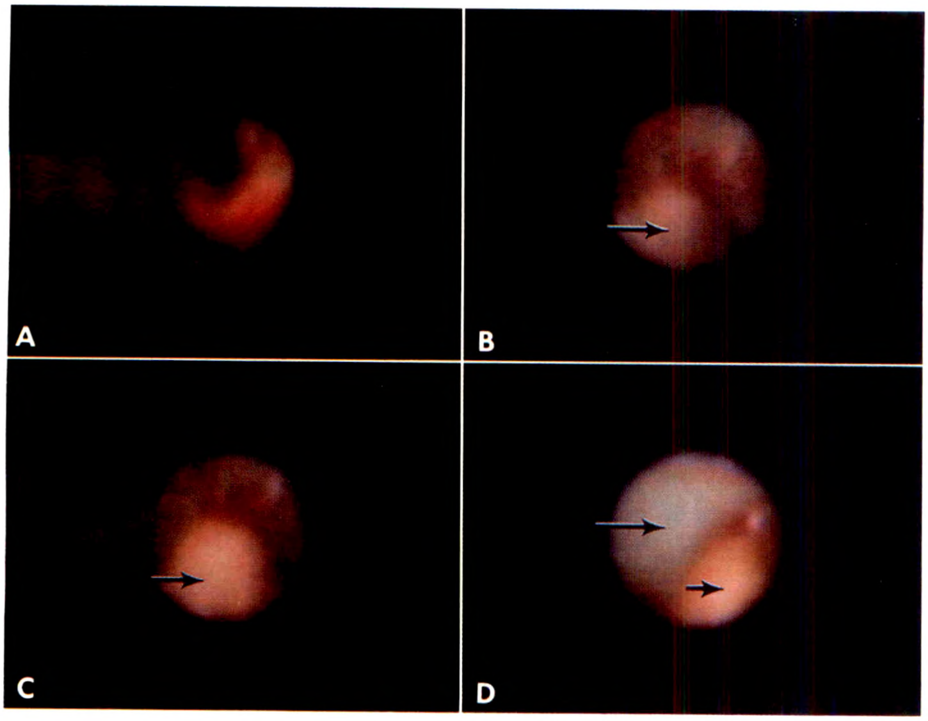

Fig 4. (Case 4) A) Following removal of single-channel electrode, scala tympani lumen is open at 2 mm. Note irregular soft tissue. B,C) At 3 mm, lumen is narrowed by fibrous sheath (arrow) that had surrounded prior electrode. D) Basilar membrane appears normal (long arrow) with fibrous sheath in lumen (short arrow).

obstruction extending through the entire inferior segment of the basal turn of the cochlea.

During the procedure all landmarks of the promontory were obliterated by extensive chalky white otosclerosis. A wire stapes prosthesis was noted to be in place. Drilling anteriorly from a point approximately 2 mm inferior to the stapes wire and slightly posterior to it, the surgeon identified labyrinthine bone with chalky white otosclerotic bone filling its lumen. Figure 2 demonstrates the irregular otosclerotic bone at different depths in the cochlea as shown through the endoscope.

Further drilling released perilymph; however, repassage of the endoscope demonstrated insufficient space at the ascending turn to allow passage of the cochlear implant electrode. For this reason, further drilling was undertaken. The passage was opened wide enough to allow the electrode to pass. All 32 rings of the electrode array were then easily passed and the patient has developed measurable open set speech discrimination.

Case 3. A 68-year-old man, deaf from an unknown cause for a period of 3 years, underwent a complete cochlear implant evaluation and was found to be an appropriate candidate. The HRCT demonstrated hard bony obstruction of the inferior segment of the basal turn. Figure 3A,B demonstrates hard bone filling the scala tympani at 4-mm and 6-mm depths of a tunnel that was drilled just anterior and inferior to the round window niche. Note the difference in appearance of this hard bone from the soft irregular otosclerotic bone in case 2. A potassium-titanyl phosphate laser was used with a 3-mm fiber bundle passed adjacent to the endoscope to clear remaining bone and open the basal turn. Figure 3C,D demonstrates the entire membranous basal turn following bone removal, including both scala tympani and scala vestibuli. Thirty-two rings of the electrode array were inserted in the scala tympani without difficulty and the patient has developed measurable open set speech discrimination.

Case 4. A 43-year-old man was thought to be deafened in the right ear by rubella as a child. The left ear then was deafened during removal of an acoustic neuroma. A previously placed single-channel electrode was removed and a 22-channel electrode inserted in the right ear. Figure 4 demonstrates the roughened, edematous, irregular basilar membrane as well as the fibrous capsule that surrounded the single-channel electrode prior to its removal. Twenty-seven rings of this patient's electrode array were inserted and the patient has developed measurable open speech discrimination.

The remaining four cases are summarized in the Table.

DISCUSSION

The previous cadaver study[8] demonstrated several obvious drawbacks to the flexible fiberoptic otologic endoscope. It is not flexible enough to pass around the turns of the cochlea. This limitation decreases its effectiveness and increases its potential for causing damage. In this study it is clear that the images obtained are useful although somewhat marginal in clarity. Both of these problems await improvements in technology.

Endoscopy of the lower airway and digestive tract has long been recognized to be valuable. More recently, endoscopy of the sinuses has also been used with success. In this series, it has been demonstrated that endoscopy of the cochlea during cochlear implantation may be used to evaluate the extent and type of obstruction and to determine patency of the cochlea after removal of the obstruction.

Identification of normal and certain pathologic features, such as otosclerosis and a fibrous sheath that remained in place after removal of the electrode that it surrounded, is possible.

The potential for use of this device in the functioning cochlea for diagnostic or surgical purposes remains unknown and will await animal studies currently planned.

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TITRATION STREPTOMYCIN THERAPY FOR BILATERAL MENIERE'S DISEASE

FOLLOW-UP REPORT

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Initial reports of the use of parenteral streptomycin for bilateral Meniere's disease (MD) have demonstrated success in reducing the vestibular symptoms and, in some patients, stabilizing hearing. The long-term follow-up (mean, 5.1 years) of 19 patients treated with intramuscular streptomycin for bilateral MD is presented. The amount of streptomycin administered (5 to 50 g) was determined by clinical symptoms and by serial testing of the reduction in the slow-phase velocity on electronystagmography. Episodic vertigo was totally relieved in 12 patients and improved in severity and frequency in an additional 4 patients. Permanent posttreatment dysequilibrium occurred in 47% of the patients treated. The changes in hearing (speech reception threshold) were independent of the therapeutic effect of streptomycin on the vestibular system. The overall results suggest that the intramuscular titration of streptomycin should continue to be considered as one of the therapeutic options in patients with disabling vertigo due to bilateral MD.

KEY WORDS — Meniere's disease, streptomycin.

INTRODUCTION

Attempts to control the disabling vertigo in patients with bilateral Meniere's disease (MD) have included the use of parenteral streptomycin. The use of this medicine has had various degrees of success, but the length of follow-up in most reports has been limited.[1-12] As the vertiginous episodes of MD are capricious in both frequency and severity, longer follow-up after streptomycin use is needed to determine the ultimate benefit of this therapy. This present report details our continuing experience with titration streptomycin therapy for patients with bilateral MD with regard to the control of the episodic vertigo, the occurrence of posttreatment dysequilibrium, and the stabilization of hearing.

MATERIALS AND METHODS

The medical records of 30 patients with bilateral MD who were treated with parenteral streptomycin were reviewed, and 19 patients were identified who had at least a 2-year minimum follow-up. The dosage and titrated administration of the streptomycin was given in the manner that has previously been described.[11] All patients had audiograms prior to treatment and these were compared to the audiogram 1 to 6 months after treatment and at the most recent follow-up examination. A change in hearing of at least 10 dB in the speech reception threshold was considered significant. The level of the pretreatment and posttreatment dysequilibrium is defined as follows: mild — unsteadiness in the dark or with quick head motion; moderate — unsteadiness in normal daily activities; and severe — oscillopsia.

RESULTS

The study population of 19 consisted of 7 men and 12 women. The average age at time of treatment was 52.8 years (range, 26 to 78 years). The amount of streptomycin titrated ranged from 5 g to 50 g (mean dose, 27.3 g). The mean follow-up of the study population was 5.1 years (range, 2 to 9.3 years). All had bilateral MD; however, 4 patients had hearing in only one ear prior to treatment.

The episodic vertigo was relieved in 18 of the 19 patients within the first 6 to 18 months after streptomycin treatment. There was total relief of vertigo in 12 patients at the last follow-up. It was improved in an additional 4 patients, with a marked decrease in the frequency and severity of their vertigo attacks. Two patients had a return of episodic vertigo, and in one patient, vertigo persisted despite treatment.

Posttreatment dysequilibrium developed in 15 of the 19 patients treated with streptomycin early on. Long-term posttreatment dysequilibrium persisted in 7 of the 12 patients who were cured of their vertigo. This dysequilibrium was mild in 5 patients and severe in 2 patients. None of the 4 patients who had improvement of their vertigo suffered from long-term posttreatment dysequilibrium. Of the 3 patients who were unchanged, 2 experienced posttreatment dysequilibrium. Posttreatment dysequilibrium in 1 patient was mild, and in another, it changed from mild to severe after treatment with streptomycin. Overall, severe dysequilibrium (ie,

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TABLE 1. POSTTREATMENT HEARING RESULTS

	Better-hearing Ear (N = 19)		Worse-hearing Ear (N = 19)	
	Short-term	*Long-term*	*Short-term*	*Long-term*
Better	4	5	3	3
Same	9	7	12	10
Worse	6	7	4	6

oscillopsia) developed in 4 patients after treatment and persisted in 3 patients.

The short-term and long-term hearing results after treatment are divided between the better-hearing and the worse-hearing ears (Table 1). Five patients noted long-term improvement in hearing in their better-hearing ear and three in their worse-hearing ear.

DISCUSSION

Vertigo due to bilateral MD is frequently disabling and difficult to treat. A nondestructive surgical procedure such as an endolymphatic sac operation could be performed bilaterally. Although most authors report a 50% to 70% incidence of relief of vertigo in unilateral MD, Glasscock et al[13] have shown it not to be of long-term benefit. Ablative surgical options (eg, vestibular nerve section or labyrinthectomy) can readily relieve vertigo in unilateral MD.[14-16] However, in bilateral MD the symptoms may emanate from both ears, the worse-hearing ear, or the better-hearing ear, thereby limiting the surgical options, although vestibular nerve section has been performed by Fisch[17] in bilateral MD. Bilateral vestibular nerve section would result in oscillopsia. The authors consider a vestibular nerve section to be relatively contraindicated in a better-hearing ear and absolutely contraindicated in an only-hearing ear because of the risk to hearing. Thus, the treatment for disabling vertigo in bilateral MD has been directed toward the use of streptomycin in order to produce a partial or total chemical labyrinthectomy without compromise of hearing.

Streptomycin was first isolated from the soil actinomycete *Streptomyces griseus* in 1944, and was initially intended for use as an antimicrobial agent. Unlike dihydrostreptomycin, streptomycin sulfate was noted to have much less cochleotoxic effect than vestibulotoxic effect.[18] Clinically, this creates a vestibular paresis while preserving hearing.[9-11,19] Studies in cats have suggested that streptomycin causes damage to the crista of the semicircular canals, with sparing of the otolithic organs.[20,21] However, there has been some speculation that the beneficial effects of streptomycin may be due to a decreased production of endolymph.[9] In addition, streptomycin may also have a central effect (ie, on the vestibular nuclei). This central effect may be a secondary change due to the peripheral end-organ damage.[18,19]

The use of streptomycin for bilateral MD was first documented by Fowler.[1] Since then, multiple reports have noted the benefit of this therapy (Table 2[1-10,12]). The initial studies concentrated on the total ablation of the vestibular system in an attempt to cure the episodic vertigo.[1-8] This, however, resulted

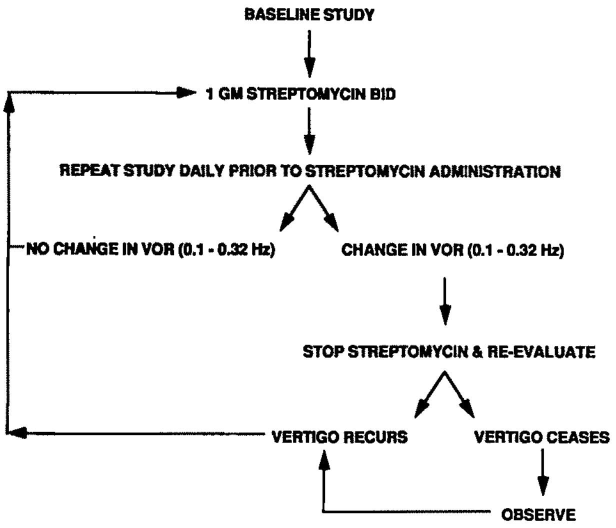
TABLE 2. SUMMARY OF STREPTOMYCIN USE FOR MENIERE'S DISEASE

	Authors	*No. of Pts*	*Total Dose (g)*	*Total Relief of Vertigo (%)*	*Residual Dysequilibrium (%)*	*Hearing (No. of Pts)*	*Follow-up (y)*
Ablation							
	Fowler[1]	4	25-33	50	50	Unchanged 2, NR 2	0.5-1
	VanDeinse[2]	3	40-56	66	NR	NR	0.3
	Hamberger et al[3]	4	55-90	100	50	Unchanged 3, improved 1	0.2-0.5
	Hanson[4]	5	40-86	60	60	Unchanged 2, improved 3	1.5-4
	Ruedi[5]	3	8-40	66	0	NR	0.2-0.5
	Von Günther[6]	8	30-58	100	NR	Improved 8	Up to 3
	Jatho[7]	2	30-61	100	NR	Unchanged 2	10
	Wilson and Schuknecht[8]	20	13.5-89	95	50	Worse 4,* unchanged 30,* improved 6*	1-16
Titration							
	Silverstein[9]	12†	15-54	88	25	Unchanged 8	0.1-1.1
	Graham and Kemink[10]	20	10-60	90	55	Unchanged 15, improved 5	1-5
	Moretz et al[12]	7	20-70	100	64	Unchanged 6, improved 1	0.5-3.5
	Present study	19	5-50	63	47	Worse 13,* unchanged 17,* improved 8*	2-9.3

NR — not reported.

*Reported in number of ears.

†Only eight treated for vertigo with intramuscular streptomycin.


BASELINE STUDY
1 GM STREPTOMYCIN BID
REPEAT STUDY DAILY PRIOR TO STREPTOMYCIN ADMINISTRATION
NO CHANGE IN VOR (0.1 - 0.32 Hz)
CHANGE IN VOR (0.1 - 0.32 Hz)
STOP STREPTOMYCIN & RE-EVALUATE
VERTIGO RECURS
VERTIGO CEASES
OBSERVE

Rotary chair algorithm for titration streptomycin therapy. BID — twice a day, VOR — vestibulo-ocular reflex.

in a high incidence of persistent and severe posttreatment dysequilibrium in some series. In addition, although there was a high cure rate in the limited number of patients reported, the follow-up periods were extremely short. Only Wilson and Schuknecht[8] had lengthy follow-up in those patients treated with ablative doses of streptomycin. More recently reports have described the use of streptomycin in lower doses.[9-11] This subtotal ablative or titration therapy technique attempts to preserve some vestibular (semicircular canal) function in order to prevent persistent posttreatment oscillopsia. This method has proven to be successful in the majority of patients treated in this manner.[9-12]

The long-term cure rate of episodic vertigo in our patients treated with titrated doses of streptomycin is similar to that of patients treated with ablative doses of streptomycin (Table 2[1-10,12]). Six patients who had relief of their vertigo initially following streptomycin treatment redeveloped vertigo. This occurred within the first 18 months following treatment. The vertigo that recurred was improved in four patients and unchanged in two patients. Patients who were relieved of their vertigo for more than 2 years after treatment with streptomycin did not develop recurrence.

In most of the patients, long-term posttreatment dysequilibrium was absent or mild. Severe posttreatment oscillopsia occurred in four patients and persisted in three patients. One patient developed oscillopsia early in our experience with streptomycin. His vestibular response was inadvertently ablated. A second patient who developed oscillopsia was noted to have a marked reduction in her vestibular response. One patient complained of oscillopsia despite persistent, reproducible caloric responses. Use of a more conservative drug titration regimen since that time has avoided this troublesome problem.[10]

Clinically there appears to be a delicate balance required to eliminate vertigo while avoiding dysequilibrium after the use of streptomycin. In many cases, patients' reports of decreased frequency and severity of vertigo, improvement of hearing, or decrease of fullness in the ear directed the dosage of streptomycin. Use of the rotary chair, which we currently employ to monitor titration therapy (see Figure), may be of more benefit in predicting a satisfactory outcome. The rotary chair can measure the vestibular-ocular reflex (VOR) across a portion of the physiologic range of head motion and is more sensitive to changes than the isothermal calorics of electronystagmography. Black et al[22] have noted that the ability to recover from ototoxic injury was greatest in those patients who had preservation of middle and high frequencies of their VOR even with the total loss of calorics (low-frequency VOR) on electronystagmography.[22]

Prior reports have alluded to the ability of streptomycin to stabilize or improve the hearing in patients with MD.[8,11] Silverstein[9] has used streptomycin to treat patients with fluctuating hearing without vestibular symptoms with mixed results during a limited follow-up period. In our patient population, changes in hearing were not correlated with improvement in vestibular symptoms. There were patients who had continued vertiginous spells but noted improvement of hearing in one or both ears, and conversely, patients with hearing deterioration who were cured of vertigo. One patient whose vertigo was improved eventually developed bilateral profound sensorineural hearing loss. Frequently, patients who had fluctuation of hearing prior to streptomycin treatment continued to have fluctuation after treatment.

Serious side effects (other than oscillopsia) were not seen from the administration of streptomycin.[23] Transient mild side effects have occurred in only a minority of patients treated. Side effects encountered include circumoral and distal extremity paresthesias, nausea, and skin rash. The occurrence of these side effects did not preclude but in some cases delayed the completion of therapy.

CONCLUSION

The majority of patients with bilateral MD treated with titration streptomycin therapy followed over the long term will have either improvement or cure of their disabling vertigo. Persistent posttreatment dysequilibrium occurs commonly; however, it is mild in the majority of patients. Stabilization or improvement of hearing occurs in a majority of patients, although changes in the speech reception threshold were independent of the therapeutic effect of streptomycin on the vestibular system.

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OBJECTIVE VOICE MEASUREMENTS & STANDARDS

A course entitled Objective Voice Measurements & Standards will be held July 22-23, 1991, at the Warwick Hotel in Philadelphia, Pennsylvania. For further information, contact The Voice Foundation, 1721 Pine Street, Philadelphia, PA 19103; (215) 735-7999.

Ann Otol Rhinol Laryngol 99:1990

IMAGING CASE STUDY OF THE MONTH

RETROPHARYNGEAL ABSCESS CAUSED BY A TRAUMATIC PERFORATION OF THE HYPOPHARYNX BY A FISHBONE

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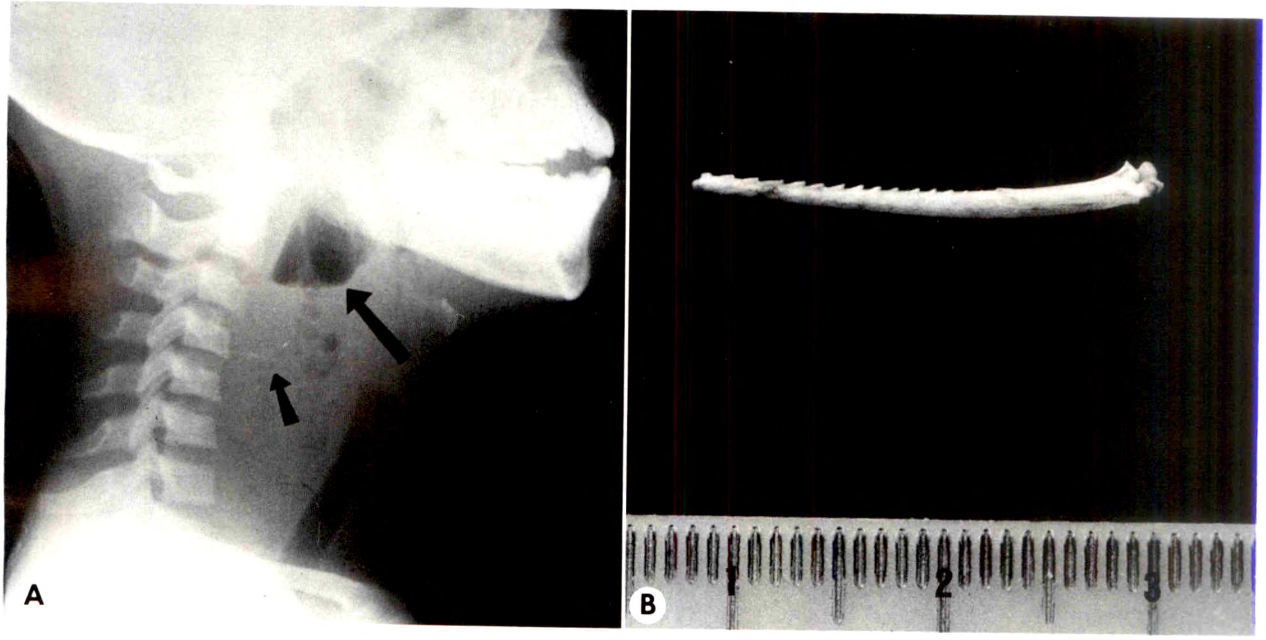
CASE REPORT

A 12-year-old girl was admitted to J. F. Kennedy Medical Center, Monrovia, Liberia, with dyspnea, dysphagia, fever, and neck pain. Five days earlier the girl had eaten fish and since then she had suffered a sharp pain during swallowing, increasing dyspnea, and tenderness in the neck. On examination at that hospital by the authors, the patient was in respiratory distress, with a temperature of 39°C. A marked tenderness was found in the upper right side of the neck. Indirect laryngoscopy revealed a bulging of the posterior hypopharyngeal wall, but no foreign body was seen.

A lateral soft tissue radiograph of the neck (see Figure, A) demonstrated a large retropharyngeal swelling with an air-fluid level and calcification and anterior displacement of the trachea. This was interpreted as a retropharyngeal abscess due to a stuck fishbone.

The patient was taken immediately to the operating room, where she developed a respiratory arrest. Since the attempts to intubate her failed, an urgent tracheotomy was performed. Thereafter, while the patient was under general anesthesia, an endoscopy revealed a bulging of the posterior hypopharyngeal wall, but no foreign body could be found either there or in the esophagus. A small incision was made in the hypopharyngeal mucosa and 20 mL of pus was drained, but again no foreign body was seen. Therefore, assuming that the foreign body perforated the pharyngeal wall, we decided to explore the neck. Through an incision anterior to the upper third of the right sternocleidomastoid muscle, a dissection was done toward the lateral pharyngeal space and from there to the retropharyngeal space, from which more pus was drained. The foreign body was palpated and removed from the retropharyngeal area (see Figure, B). A Penrose drain was left in this space and a nasogastric tube



A) Lateral radiograph of neck showing retropharyngeal air-fluid level (long arrow) and calcified foreign body (short arrow). B) Photograph of foreign body after its extraction. Scale is in centimeters.

From the Ear, Nose, and Throat Department, Hadassah University Hospital, Jerusalem, Israel.

was introduced. The postoperative course was uneventful and after a week the tracheotomy was closed and the girl started to eat normally.

DISCUSSION

Retropharyngeal abscess is usually a disease of young children.[1] It occurs after an upper respiratory tract infection with necrosis and suppuration of the lymph nodes in the retropharyngeal space. These nodes drain the nasal airway, eustachian tube, sinuses, and pharynx. The other two common causes are tuberculosis of the cervical spine (Pott's disease) and a perforating foreign body.[2] Usually there is a history of upper respiratory tract infection or swallowing of a foreign body.

A retrospective study (36 years' experience at Children's Hospital of Los Angeles) revealed 65 children with a retropharyngeal abscess. The most common causes were laryngotracheal bronchitis and tonsillitis. No child was found with a retropharyngeal abscess due to a foreign body.[3]

The clinical picture is quite typical. The child is ill with a high fever, dysphagia, dyspnea, and a muffled cry, which are evident when the swelling becomes large enough.

Physical examination reveals a cervical adenitis and a bulging of the posterior pharyngeal wall, and sometimes a neck swelling is palpable.[2,4] A lateral soft tissue radiograph of the neck demonstrates widening of the retropharyngeal space with displacement of the trachea, an air-fluid level, and sometimes a foreign body.

Treatment should not be delayed. The patient should be given intravenous antibiotics. Drainage is indicated as soon as possible and removal of a foreign body is performed, usually through the incision in the hypopharyngeal wall.[2,4] Intubation may be difficult and rupture of the abscess may occur. A large abscess needs drainage through the neck by dissection medial to the anterior border of the sternocleidomastoid muscle.[4]

To the best of our knowledge this is the first case in the English-language literature in which a perforating hypopharyngeal foreign body was successfully removed through a neck incision.

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Ann Otol Rhinol Laryngol 99:1990

PATHOLOGY CONSULTATION

HISTOPATHOLOGIC GRADING OF SALIVARY GLAND NEOPLASMS: II. ACINIC CELL CARCINOMAS

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Acinic cell carcinomas display varied cytoarchitectural patterns of growth that should allow for formulation of histopathologic grading. Grading of these carcinomas may serve to identify subsets whose biologic behavior is more aggressive than the usually accepted low-grade behavior of acinic cell carcinomas as a group. To that end, a three-level histopathologic grading scheme is presented.

Acinic cell carcinomas have, like mucoepidermoid carcinomas, overcome a not-too-remote ambiguity concerning their malignant potential (Tables 1[1] and 2). Repeated documentations of the malignancy of acinic cell carcinomas[1-6] have finally put to rest peculiar academic semantics that fostered statements such as "There are only occasional facultative malignant variants of acinic cell neoplasms... The number of cases that ultimately become malignant and metastasize is so small that these tumors are not entitled to be grouped all together under the generic term acinic cell carcinomas. Neither are they to be regarded as semimalignant growths."[7]

Acinic cell carcinomas do not arise from differentiated and functionally mature acinar cells by "dedifferentiation." They originate as a result of the neoplastic proliferation and aberrant cytodifferentiation of pluripotential reserve or stem cells that normally reside at the acinar–intercalated duct junctions and/or in the intercalated ducts proper of mature salivary glands.[8-11] In the process, the acinic cell carcinoma is the prime example supporting the concept that differentiated salivary gland tumors recapitulate various developmental stages in the normal embryogenesis of salivary glands.[10]

In its highest phenotypic expression, the acinic cell carcinoma conveys a seemingly innocuous appearance, and the similarity between normal parotid acinar cells and the carcinoma cells is apparent. In such well-differentiated carcinomas, the ultrastructural and biochemical features of the carcinomas also show a striking similarity to those of normal parotid tissue, even to cells possessing an intact secretory apparatus that can release amylase.[12]

TABLE 1. MORBIDITY AND MORTALITY OF ACINIC CELL CARCINOMA

Source	*Recurrence Rate (%)*	*Metastatic Rate (%)*	*Death Rate (%)*
Armed Forces Institute of Pathology (N = 244)	12	7.8	6.1
Combined literature sources (N = 367)	35	55	16

Information from Ellis and Corio.[1]

Acinic cell carcinomas manifest several architectural growth patterns: solid-lobular, acinar-microcystic, papillocystic, tubuloductal, follicular, and "dedifferentiated."[2,3,13] The first two are the most common and are also the patterns that most closely resemble the lobular arrangements of a normal parotid gland (Fig 1A,B). Either of the patterns is usually present with the other types. In that respect, the solid undifferentiated ("dedifferentiated") acinic cell carcinoma (Fig 1C) cannot be recognized as such without fields displaying other growth patterns, most often acinar-microcystic and tubuloductal (Fig 1D). The follicular acinic cell carcinoma appears to be an exaggerated acinar-microcystic

TABLE 2. SALIENT CLINICAL CHARACTERISTICS OF ACINIC CELL CARCINOMAS

Incidence in parotid gland	2.5% to 7% of all parotid epithelial tumors and 12.5% of carcinomas of parotid gland
Salivary site predilection	Almost exclusively parotid gland; rare in other major glands and in seromucous glands of upper aerodigestive tracts
Age	Fourth to sixth decade
Sex	2:1 female preponderance
Multicentricity in parotid gland	2% to 5%
Bilaterality in parotid glands	Ranks second to Warthin's tumors and first among salivary carcinomas
Intranodal (parotid and periparotid) origin	Estimated frequency of 10%; ranks second to Warthin's tumors
Incidence in children 12 years and younger	Ranks second to mucoepidermoid carcinoma for malignancies of parotid gland

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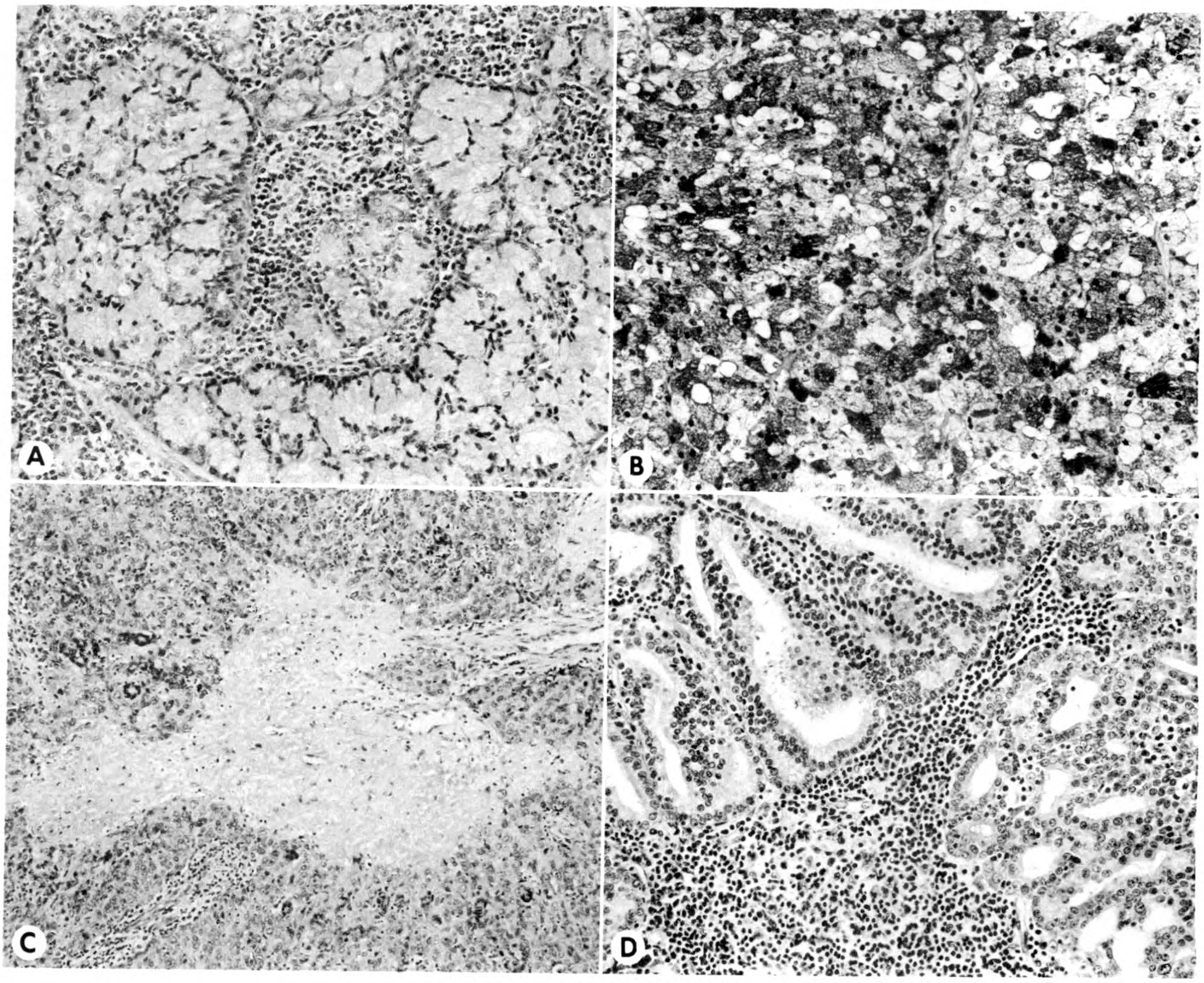

Fig 1. Acinic cell carcinoma of parotid gland. A) Well-differentiated (H & E, original x200). This carcinoma took its origin from enclaved salivary tissue in parotid lymph node and was confined to lymph node. B) Well-differentiated, with lobular architecture (H & E, original x170). Note dark (basophilic) cytoplasmic granules that have led to term "blue dot tumor." C) High-grade (grade 3; H & E, original x100). This field shows central necrosis and "dedifferentiated" cytomorphology of carcinoma. D) With tubulo-ductal differentiation placing it into grade 2 category (H & E, original x200).

pattern wherein dilated acini, lined by a flattened epithelium, contain a watery or colloid-like intrafollicular fluid (Fig 2A). In its fullest development, a follicular acinic cell carcinoma resembles thyroid gland. We believe papillocystic acinic cell carcinomas have two forms of genesis: one, a retrogressive phenomenon; the other, solely neoplastic. The former is the more common and is a histopathologic reflection of a self-destructive quality of some acinic cell carcinomas, the end stage of which is a solitary, sometimes loculated cyst (Fig 2B) with attenuated and hydropically altered neoplastic cells in company with neoplastic papillary excrescences in various stages of degeneration (Fig 2C). Compromise of the carcinoma's microvasculature is the initiating and perpetuating event in the following sequence: 1) central ischemia, 2) liquefactive necrobiosis, 3) micropapillocyst formation, 4) continuing necrosis (with or without hemorrhage) of micropapillae, 5) liberation of tissue-toxic secretory granules and lipoproteinaceous secretory product, and 6) a parvicellular solitary or loculated cyst with a variably thick encompassing fibrogranulomatous tissue reaction in which lipid crystals, foreign body giant cells, and evidence of old and more recent hemorrhage is seen (Fig 2D).

Since carcinomas do not dedifferentiate but rather fail to differentiate toward a higher phenotype, the misnamed "dedifferentiated" acinic cell carcinomas are those in which there are various proportions of synchronous or metachronous undifferentiated or poorly differentiated carcinoma.[13] They take the form of either syncytial sheets or islands of primitive cells or poorly developed, invasive ducts or tubules. These histologically higher-grade elements are usually accompanied by readily identified vascular and perineurial invasion.

Table 3 presents a histopathologic grading scheme for acinic cell carcinomas. Like that for mu-

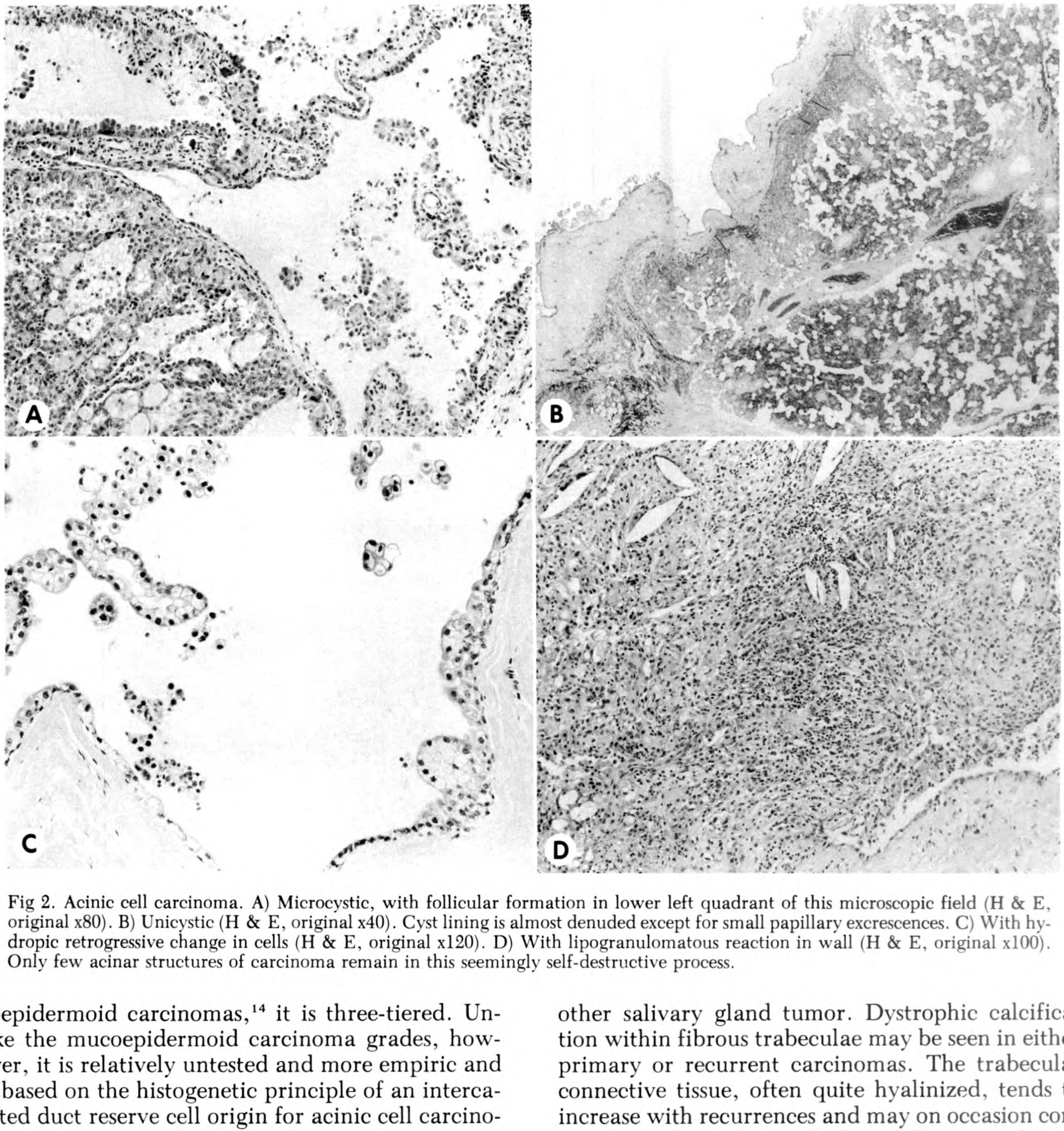

Fig 2. Acinic cell carcinoma. A) Microcystic, with follicular formation in lower left quadrant of this microscopic field (H & E, original x80). B) Unicystic (H & E, original x40). Cyst lining is almost denuded except for small papillary excrescences. C) With hydropic retrogressive change in cells (H & E, original x120). D) With lipogranulomatous reaction in wall (H & E, original x100). Only few acinar structures of carcinoma remain in this seemingly self-destructive process.

coepidermoid carcinomas,[14] it is three-tiered. Unlike the mucoepidermoid carcinoma grades, however, it is relatively untested and more empiric and is based on the histogenetic principle of an intercalated duct reserve cell origin for acinic cell carcinomas.[8-10] The more ductal or tubular elements in an acinic cell carcinoma, the higher the grade, with the undifferentiated cell mass as the histologic hallmark of the grade 3 carcinoma. Neoplastic caricatures most closely resembling normal salivary parenchyma are the grade 1 carcinomas. Transitions between grades 1 and 2 are not as sharply defined as those between the equivalent grades of mucoepidermoid carcinomas. The level of differentiation in grade 3 carcinomas, however, is an unambiguous criterion.

Other light-optic findings, including those after histochemical or immunocytochemical reactions, provide limited differential diagnostic information and no prognostic information. Calcospherites are found in acinic cell carcinomas more often than any other salivary gland tumor. Dystrophic calcification within fibrous trabeculae may be seen in either primary or recurrent carcinomas. The trabecular connective tissue, often quite hyalinized, tends to increase with recurrences and may on occasion contain metaplastic bone. Vulnerability to ischemia and/or retrogressive liquefactive changes can lead to liberation of tissue-toxic secretory products producing a profound lipidic-mucoid-granulomatous reaction rivaled only by that seen with mucoepidermoid carcinomas and ruptured Warthin's tumors.

The term "blue dot tumors" has been applied to acinic cell carcinomas because of a sometimes intense basophilism of cytoplasmic granules (Fig 1B). Basophilic granules are not reliable criteria, and in our experience a "blue dot" acinic cell carcinoma is uncommon. Much more often the granular cytoplasm is amphophilic or even palely eosinophilic.

Optically clear or vacuolated acinic cell carcinoma cells are often seen, but do not qualify the carci-

TABLE 3. HISTOLOGIC GRADING OF ACINIC CELL CARCINOMAS

Grade 1	*Grade 2*	*Grade 3*
Monolobular and circumscribed; may be encapsulated; may be intranodal in origin	Lobulated or multifocal; circumscription is less defined; no apparent capsule	Uncircumscribed, infiltrative
Less than 3 cm	3 to 6 cm	Larger than 6 cm
No deep lobe (parotid) involvement	Deep lobe (parotid) involvement	Deep lobe (parotid) involvement or extraparenchymal extension
Dominance of differentiated solid, acinar, or microcystic architecture; macrocystic (retrogressive) forms	Tubuloductal differentiation (intercalated duct-like) of more than 15% to 20% of architecture; neoplastic, as opposed to retrogressive, papillocystic architecture	Undifferentiated, syncytial sheets with or without less-differentiated tubuloductal infiltrative patterns; cyst formation is uncommon; never macrocystic
Minimal or no nuclear or cellular pleomorphism; no mitoses; necrosis is absent except for that related to retrogressive macrocyst formation; no invasive properties	May have foci with nuclear and cellular pleomorphism; mitoses are scant; solid areas may show coagulative or hemorrhagic necrosis; invasion of small nerves, but never prominent; endovascular extension can be seen	Cellular constituents are histologically malignant, either undifferentiated with numerous mitoses or invasive with poorly developed tubuloductal formations; prominent invasion of large and small nerves and vessels

noma as a specific variant. There is no clear cell acinic cell carcinoma. Optical clarity is a result of one or more of three causes: 1) optically clear granules, 2) hydropic degeneration, and 3) postremoval artifact.

The number and developmental stage of the secretory granules also account for staining differences with periodic acid–Schiff reagents, and that staining reaction should never be used alone for diagnosis. In addition, any acinic cell carcinoma, regardless of salivary site, can manifest cells, and certainly extracellular fluids, stainable for mucin.

In differentiated acinic cell carcinomas, immunoreactions for amylase, lactoferrin, secretory piece, and proline-rich protein are positive. The intensity and distribution of the reactions vary not only between carcinomas, but also within areas of a single carcinoma. Antikeratins are usually not positive. Myoepithelial cells are usually not identified, and if they are, they appear to be passive participants and not integral to the phenotype of acinic cell carcinomas.

Only in unusual circumstances will ultrastructural study be necessary to make a diagnosis of acinic cell carcinoma. Erlandson and Tandler,[15] Bloom and Henriksson,[16] and Chaudhry et al[11] describe "classic" as well as less-classic forms. Their studies affirm the following: 1) "clear cells" in acinic cell carcinomas are those with ghost granules from which core material has been partially or completely lost through autophagy; 2) even in typical acini, secretory granules vary in size, shape, and electron density; and 3) intercalated ducts also contain granules resembling those of acini.

Why three grades instead of only high-grade and low-grade classifications? The three-tiered system does the following: 1) recognizes the copulative role of the intercalated duct–like structures to either the more- or less-differentiated cellular constituents, 2) appreciates that the number of published examples of grade 3 carcinomas is too small for irrefragable conclusions on biologic behavior, especially if comparisons are to be made with grade 3 mucoepidermoid and the high-grade salivary duct carcinomas, and 3) maintains a numeric symmetry with the grading of mucoepidermoid[14] and adenoid cystic[17] carcinomas.

Whether DNA cytophotometry can provide significant prognostic information beyond that provided by histopathologic evaluation alone is unclear. Gustafsson et al,[18] using single cell cytophotometry, concluded that the nuclear DNA patterns of acinic cell carcinomas were of minor importance with regard to survival time and potential for metastasis. Hamper et al[19] have indicated similar findings with DNA cytophotometry on acinic cell carcinomas. As yet, there are no published data from *flow* cytometric studies on the carcinomas. Preliminary work in our laboratories, however, indicates that flow, in contrast to single cell, cytometry may be a valuable adjunct in predicting outcome.

The Memorial Sloan-Kettering Cancer Center's experience with acinic cell carcinomas, in aggregate, indicates that about 85% of its patients with that neoplasm are alive at a 10-year follow-up — the best survivorship of all carcinomas of salivary glands.[20,21] The relatively low metastatic rate of the carcinomas (Table 4[21]) supports these observations. Survival was most directly influenced by the clini-

TABLE 4. METASTATIC BEHAVIOR OF CARCINOMAS OF MAJOR SALIVARY GLANDS

	Percent Metastasizing to	
Histopathologic Classification	*Lymph Nodes*	*Distant Sites*
Low-grade (grade 1) mucoepidermoid carcinoma	3	0
Acinic cell carcinoma	7	5
Adenoid cystic carcinoma	8	32
Carcinoma ex pleomorphic adenoma	19	16
Adenocarcinoma	39	26
Intermediate-grade and high-grade mucoepidermoid carcinomas	44	23
Squamous cell carcinoma	58	42
Anaplastic undifferentiated	83	50

From data presented by Spiro et al[21] and based on 439 cases.

cal extent (stage) of the primary, but there was also a correlation with certain histopathologic features graded into three groups.[4] Groups 1 and 2 were separated only on the basis of invasion of a tumoral capsule and blood vessels. The third group is described as a papillary-cystic pattern. Patients with carcinomas in groups 2 or 3 more often had locally advanced disease. Survival curves based on these histologic criteria alone seemed to show significant differences — mitigated, however, by the fact that the numbers of patients in any group did not exceed 38 and group 3 had only 5 patients.[4] Such findings nonetheless suggest that histopathologic grading of acinic cell carcinomas is capable of identifying subsets whose clinical courses are better or worse than those that collective groupings convey.

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BOOK REVIEWS

Physiology of the Ear

Anthony F. Jahn and Joseph Santos-Sacchi, editors. Hard cover, illustrated, indexed, 539 pages, 1988. Raven Press, New York, NY, $99.

It took scientists like George von Bekesy over 50 years to qualify Hermann von Helmholz's theories of cochlear function. As much time has lapsed since von Bekesy pioneered work in the psychoacoustics of the external auditory canal and middle ear and introduced his traveling wave theory. Much has been done in the interim, and a review of *Physiology of the Ear*'s extensive bibliography reveals that a plethora of work has been done in this decade. Although von Bekesy's fundamental principles of the traveling wave theory still stand, evidence suggests that pure tone stimulation of the basilar membrane is dependent on a series of inducers in the transmission line model of the cochlea. This is also flawed because of the inability to explain increased frequency selectivity with steeper high-frequency slopes. The nonlinearity of the basilar membrane was also not understood until more recent studies. The authors perceptively include this information in the text.

The real substance of *Physiology of the Ear* is to be found in the chapters The External Ear, Introduction to the Analysis of Middle Ear Function, Cochlear Signal Processing, Cochlear Physiology, The Physiology of the Cochlear Nerve, and Introduction to Anatomy and Physiology of the Central Auditory System. The authors of these chapters convey their material in a readable and, for the most part, understandable fashion. Support chapters include several predominately dealing with microscopic anatomy of the temporal bone and its structures. One chapter on otoimmunity of the middle ear mucosa is included.

A very clinical chapter on the physiology of the eustachian tube includes the discussion of difficult-to-diagnose conditions, difficult-to-treat symptoms, autophonia, and hyperacusis. Attempts to analyze or explain such complex situations typically raise more questions; the authors did well in anticipating and answering many of these. The introduction to the book by Joseph E. Hawkins, Jr, is a historical sketch of auditory physiology (ancients to von Bekesy) that stimulates interest with the promise of future advances on cochlear mechanics and otoneurochemistry.

One is not to be misled into thinking that physiology of the vestibular system is included in this volume. There is only one chapter, on functional morphology, related to it. The main thrust of this book is on hearing physiology.

With today's interface between physician, research scientist, and engineer, there is a need for information that is comprehensive and functional. *Physiology of the Ear* would make a good reference book, since it is chronologically complete and practical.

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The Biology of Hearing and Deafness

Robert V. Harrison. Hard cover, illustrated, indexed, 432 pages, 1988. Charles C Thomas, Publisher, Springfield, Ill, $67.50.

What are considered today to be the main anatomic structures of hearing (tympanic membrane, ossicles, cochlea, etc) have been frequently described in the literature to the extent permitted by the technology available. The revelation of how limited these descriptions probably are comes about in Part I of this book, and may be its most significant contribution. Dr Harrison's use of scanning photomicrography divulges intimate details of the cochlea that stimulate an appetite to learn more about their intricate compositions and a realization that the actual physiologic and mechanical process of hearing remains one of the least-understood phenomena. The author takes good advantage of the space allowed in a volume to accompany each photomicrograph with a careful description of its contents. For the practicing otolaryngologist who wishes to review and understand cochlear mechanics, including the pinna and ear canal, middle ear, and cochlea, the author provides a simple explanation.

Part II of this book focuses on deafness resulting from cochlear disease. Conductive losses and those caused by disorders in the central pathways are not addressed. Primarily, Dr Harrison reports on hearing losses resulting from acute and chronic insults to the cochlea. A clear overview of the pathophysiology of ototoxicity, acoustic trauma, hypoxia and the effects of temperature on the inner ear is nicely presented. As befits a section devoted to the results of research, the author presents an extensive and useful review of the literature.

This volume has dual value: 1) as a record of current knowledge provided in excellent coverage of new work, and 2) as a stimulating overview of the diverse strategies currently being applied to the problems of deafness. If it is reviewed by chapter, deficiencies in its coverage of some conditions, such as presbycusis, hereditary deafness, and Meniere's disease, will become obvious. This is not the fault of the author, however; there is just less "biologic" information available on these subjects than on ototoxicity, acoustic trauma, or hypoxia.

Dr Harrison has, overall, done a fine job in clarifying a very complex subject. In addition to use by the otolaryngologist, this book will serve as an excellent reference for all those engaged in the disciplines involved in the biology of hearing and deafness.

DENNIS G. PAPPAS, MD
Birmingham, Alabama

Musculocutaneous Flap Reconstruction of the Head and Neck

William R. Panje, David E. Schuller, and Frank W. Shagets. Hard cover, illustrated, indexed, 244 pages, 1989. Raven Press, New York, NY, $110.

The 1980s saw the rapid development of reconstructive options in the head and neck region following surgical procedures for cancer extirpation. The hallmarks of these advances are represented by the musculocutaneous and the microvascular free flaps. These techniques entail the additional ability to provide repair of osseous defects when needed. Drs William R. Panje, David E. Schuller, and Frank W. Shagets have compiled a well-organized, readable edition on musculocutaneous flaps in the head and neck.

The first section of the book includes a chapter on flap physiology. An especially clinically relevant section deals with the "dying" flap. Separate chapters are devoted to the different musculocutaneous flap types, including the commonly used pectoralis and trapezius flaps; the temporalis flaps, assuming importance in skull base defects; the less commonly employed but quite functional latissimus dorsi and sternocleidomastoid flaps; and the highly specific orbicularis oris and platysma flaps. These chapters contain informative narratives followed by the authors' comments. The photographs are helpful, but more specific serial diagrams would provide the reader with more clarity concerning actual surgical technique.

The second section is broken down by chapter according to anatomic site and defect. The authors provide reconstructive alternatives based on location and size of defect and, in the case of mandible reconstruction, means of providing osseous repair. Once again, copious photographs are available, but the inclusion of diagrams would have added educational value, especially for the resident or attending surgeon beginning to master these techniques.

The text, however, is comprehensively indexed, and the first section chapters are followed by lists of sources to which the practitioner can refer if more detailed descriptions of the actual procedures are required.

This book should be part of any library where teaching institutions or private surgeons actively pursue head and neck surgery. The authors' experience in the field is extensive, and the text can confidently be referred to in planning the repair of significant surgical defects.

DAVID KAUFMAN, MD
New York, New York

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John Isaacs, MD, Chairman
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3. Frequency of Issue Monthly	3A. No. of Issues Published Annually Twelve	3B. Annual Subscription Price $85 US; $105 Foreign

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